Cochrane Database of Systematic Reviews

Antibiotics for acute laryngitis in adults (Review)

Reveiz L, Cardona AF

Reveiz L, Cardona AF.
Antibiotics for acute laryngitis in adults.
Cochrane Database of Systematic Reviews 2015, Issue 5. Art. No.: CD004783.
DOI: 10.1002/14651858.CD004783.pub5.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 3
BACKGROUND 6
OBJECTIVES 6
METHODS 6
RESULTS 9
Figure 1. 10
Figure 2. 11
DISCUSSION 13
AUTHORS' CONCLUSIONS 15
ACKNOWLEDGEMENTS 15
REFERENCES 16
CHARACTERISTICS OF STUDIES 19
DATA AND ANALYSES 22
Analysis 1.1. Comparison 1 Fusafungine versus fusafungine + clarithromycin, Outcome 1 Clinical cure rates at day 5 ± 1. 22
Analysis 1.2. Comparison 1 Fusafungine versus fusafungine + clarithromycin, Outcome 2 Clinical cure rates at day 8 ± 1. 23
Analysis 1.3. Comparison 1 Fusafungine versus fusafungine + clarithromycin, Outcome 3 Clinical cure rates at day 28 ± 2. 23
Analysis 1.4. Comparison 1 Fusafungine versus fusafungine + clarithromycin, Outcome 4 Frequency of adverse events. 23
Analysis 2.1. Comparison 2 Fusafungine versus no treatment, Outcome 1 Clinical cure rates at day 5 ± 1. 24
Analysis 2.2. Comparison 2 Fusafungine versus no treatment, Outcome 2 Clinical cure rates at day 8 ± 1. 24
Analysis 2.3. Comparison 2 Fusafungine versus no treatment, Outcome 3 Clinical cure rates at day 28 ± 2. 24
Analysis 3.1. Comparison 3 Fusafungine + clarithromycin versus no treatment, Outcome 1 Clinical cure rates at day 5 ± 1. 25
Analysis 3.2. Comparison 3 Fusafungine + clarithromycin versus no treatment, Outcome 2 Clinical cure rates at day 8 ± 1. 25
Analysis 3.3. Comparison 3 Fusafungine + clarithromycin versus no treatment, Outcome 3 Clinical cure rates at day 28 ± 2. 26
Analysis 4.1. Comparison 4 Erythromycin versus placebo, Outcome 1 Laryngitis at 1 week. 26
Analysis 4.2. Comparison 4 Erythromycin versus placebo, Outcome 2 Laryngitis at 2 week. 27
Analysis 4.3. Comparison 4 Erythromycin versus placebo, Outcome 3 Elimination rate of Moraxella catarrhalis at 1 week. 27
Analysis 4.4. Comparison 4 Erythromycin versus placebo, Outcome 4 Elimination rate of Moraxella catarrhalis at 2 week. 27
Analysis 4.5. Comparison 4 Erythromycin versus placebo, Outcome 5 Patients having voice disturbance at week 1. 28
Analysis 4.6. Comparison 4 Erythromycin versus placebo, Outcome 6 Patients having voice disturbance at week 2. 28
Analysis 4.7. Comparison 4 Erythromycin versus placebo, Outcome 7 Cough at week 1 (subjective symptom). 28
Analysis 4.8. Comparison 4 Erythromycin versus placebo, Outcome 8 Cough at week 2 (subjective symptom). 28
APPENDICES 29
FEEDBACK 33
WHAT'S NEW 35
HISTORY 36
CONTRIBUTIONS OF AUTHORS 36
DECLARATIONS OF INTEREST 36
SOURCES OF SUPPORT 37
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 37
INDEX TERMS 37

[Intervention Review]

Antibiotics for acute laryngitis in adults

Ludovic Reveiz[1], Andrés Felipe Cardona[2]

[1]Free time independent Cochrane reviewer, Potomac, MD, USA. [2]Clinical and Translational Oncology Group, Institute of Oncology, Fundación Santa Fe de Bogotá, Bogotá, Colombia

Contact address: Ludovic Reveiz, Free time independent Cochrane reviewer, Potomac, MD, USA. mmreveiz@hotmail.com, reveizl@paho.org.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 5, 2015.

Citation: Reveiz L, Cardona AF. Antibiotics for acute laryngitis in adults. *Cochrane Database of Systematic Reviews* 2015, Issue 5. Art. No.: CD004783. DOI: 10.1002/14651858.CD004783.pub5.

ABSTRACT

Background

This is an update of the original review published in 2005. Acute laryngitis is a common illness worldwide. Diagnosis is often made by case history alone and treatment often targets symptoms.

Objectives

To assess the effectiveness and safety of different antibiotic therapies in adults with acute laryngitis. A secondary objective was to report the rates of adverse events associated with these treatments.

Search methods

We searched CENTRAL (2014, Issue 11), MEDLINE (January 1966 to November week 3, 2014), EMBASE (1974 to December 2014), LILACS (1982 to December 2014) and BIOSIS (1980 to December 2014).

Selection criteria

Randomised controlled trials (RCTs) comparing any antibiotic therapy with placebo for acute laryngitis. The main outcome was objective voice scores.

Data collection and analysis

Two review authors independently extracted and synthesised data.

Main results

We included three RCTs (351 participants) that had moderate to high risk of bias. The quality of the evidence was very low for all outcomes. We downgraded the studies because of limitations in study design or execution (risk of bias), imprecision and inconsistency of results. We included a new trial presented only as a conference abstract in this update.

In one study of acute laryngitis in adults, 100 participants were randomised to receive penicillin V (800 mg twice daily for five days) or an identical placebo. A recording of each patient reading a standardised text was made at the first visit, during re-examination after one and two weeks, and at follow-up after two to six months. No significant differences were found between the groups. The trial also measured symptoms reported by participants and found no significant differences.

One study investigated erythromycin for acute laryngitis in 106 adults. The mean objective voice scores measured at the first visit, at re-examination after one and two weeks, and at follow-up after two to six months did not significantly differ between the groups. At one week there were significant beneficial differences in the severity of reported vocal symptoms (slight, moderate and severe) as judged by participants (P value = 0.042). However, the rates of participants having improved voice disturbance (subjective symptoms) at one and two weeks were not significantly different among groups. Comparing erythromycin and placebo groups on the rate of persistence of cough at two weeks, the risk ratio (RR) was 0.38 (95% confidence interval (CI) 0.15 to 0.97, P value = 0.04) and the number needed to treat for an additional beneficial outcome (NNTB) was 5.87 (95% CI 3.09 to 65.55). We calculated a RR of 0.64 (95% CI 0.46 to 0.90, P value = 0.034) and a NNTB of 3.76 (95% CI 2.27 to 13.52; P value = 0.01) for the subjective voice scores at one week.

A third trial from Russia included 145 patients with acute laryngitis symptoms. Participants were randomised to three treatment groups: Group 1: seven-day course of fusafungine (six times a day by inhalation); Group 2: seven-day course of fusafungine (six times a day by inhalation) plus clarithromycin (250 mg twice daily for seven days); Group 3: no treatment. Clinical cure rates were measured at days 5 ± 1, 8 ± 1 and 28 ± 2. The authors reported significant differences in the rates of clinical cure at day 5 ± 1 favouring fusafungine (one trial; 93 participants; RR 1.50, 95% CI 1.02 to 2.20; P value = 0.04) and fusafungine plus clarithromycin (one trial 97 participants; RR 1.47, 95% CI 1.00 to 2.16; P value = 0.05) when compared to no treatment. However, no significant differences were found at days 8 ± 1 and 28 ± 2. Also, no significant differences were found when comparing fusafungine to fusafungine plus clarithromycin at days 5 ± 1, 8 ± 1 and 28 ± 2.

Authors' conclusions

Antibiotics do not appear to be effective in treating acute laryngitis when assessing objective outcomes. They appear to be beneficial for some subjective outcomes. Erythromycin could reduce voice disturbance at one week and cough at two weeks when measured subjectively. Fusafungine could increase the cure rate at day five. The included RCTs had important methodological problems and these modest benefits from antibiotics may not outweigh their cost, adverse effects or negative consequences for antibiotic resistance patterns.

PLAIN LANGUAGE SUMMARY

Antibiotics to treat adults with acute laryngitis

Review question
Cochrane authors reviewed the available evidence from randomised controlled trials on the use of antibiotics for adults with acute laryngitis.

Background
Acute laryngitis is an inflammation of the larynx. The most common symptoms are hoarseness, fever, sore throat, postnasal discharge and difficulty in swallowing. Antibiotics are frequently prescribed by physicians or self prescribed. Reasons for over-prescribing antibiotics in upper respiratory tract infections such as acute laryngitis are varied but they often involve physicians' and patients' attitudes and expectations.

Study characteristics
This review found three studies involving 351 participants evaluating the effectiveness of different antibiotic therapies in adults with acute laryngitis. The evidence is current to December 2014.

Quality of the evidence
We ranked the quality of the evidence as low to very low, mainly because many studies had methodological limitations, outcome results were based on limited numbers of trials and the trials included participants that could not be pooled.

Key results
We found that penicillin V and erythromycin appear to have no benefit in treating acute laryngitis. Erythromycin could reduce voice disturbance at one week and cough at two weeks when measured subjectively. Fusafungine could improve the rates of cured patients at day five. Overall, there is no clear benefit for the primary outcome, which is an objective assessment of voice quality, but some improvements are seen in subjective measures (i.e. cough, hoarseness of voice) that could be important to patients. However, we consider that these modest benefits from antibiotics may not outweigh their cost, adverse effects or negative consequences for antibiotic resistance patterns. The implications for practice are that prescribing antibiotics should not be done in the first instance as they will not objectively improve symptoms

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Fusafungine compared with no treatment for acute laryngitis in adults

Patient or population: adults with acute laryngitis

Settings: ambulatory

Intervention: fusafungine

Comparison: no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	Fusafungine				
Clinical cure rates at day 8 ± 1	**Study population**		**RR 1.07 (0.88 to 1.31)**	93 (1)	⊕⊝⊝⊝ **very low** [a]	Comparing a 7-day course of fusafungine (6 times a day by inhalations) versus no treatment (Rafalskiy 2012)
	778 per 1000	**832 per 1000** (684 to 1000)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]One study with design limitations. Wide confidence interval crossing the line of no effect and small sample size. Serious imprecision and very serious risk of bias.

Summary of findings 2.

Fusafungine plus clarithromycin compared with no treatment for acute laryngitis in adults

Patient or population: adults with acute laryngitis

Settings: ambulatory

Intervention: fusafungine plus clarithromycin

Comparison: no treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No treatment	Fusafungine plus clarithromycin				
Clinical cure rates at day 8 ± 1	**Study population**		**RR 1.09 (0.90 to 1.32)**	97 (1)	⊕⊝⊝⊝ **very low** [a]	Comparing a 7-day course of fusafungine (6 times a day by inhalations) plus clarithromycin (250 mg twice a day for 7 days) versus no treatment (Rafalskiy 2012)
	778 per 1000	**848 per 1000** (700 to 1000)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]One study with design limitations. Wide confidence interval crossing the line of no effect and small sample size. Serious imprecision and very serious risk of bias

Summary of findings 3.

Erythromycin compared with placebo for acute laryngitis

Patient or population: adults with acute laryngitis

Settings: ambulatory

Intervention: erythromycin

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No. of participants	Quality of the evidence	Comments

	Assumed risk	Corresponding risk		(studies)	(GRADE)	
	Placebo	**Erythromycin**				
Laryngitis at 1 week	**Study population**		**RR 1.10 (0.76 to 1.59)**	99 (1)	⊕⊕⊝⊝ **low**[a]	Erythromycin 500 mg twice a day for 5 days Schalén 1993
	510 per 1000	**561 per 1000** (387 to 811)				
Laryngitis at 2 weeks	**Study population**		**RR 0.81 (0.44 to 1.49)**	99 (1)	⊕⊕⊝⊝ **low**[a]	—
	333 per 1000	**270 per 1000** (147 to 497)				
Patients having voice disturbance at 1 week	**Study population**		**RR 0.87 (0.59 to1.28)**	99 (1)	⊕⊕⊝⊝ **low**[a]	—
	549 per 1000	**478 per 1000** (324 to 703)				
Patients having voice disturbance at 2 weeks	**Study population**		**RR 0.56 (0.28 to 1.14)**	99 (1)	⊕⊕⊝⊝ **low**[a]	—
	333 per 1000	**187 per 1000** (93 to 380)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[a]One study with design limitations. Wide confidence interval crossing the line of no effect and small sample size. Serious imprecision and risk of bias.

BACKGROUND

Description of the condition

Upper respiratory tract infection (URTI) is the most common acute illness worldwide and is usually self diagnosed and self treated at home (Cherry 2003; McAvoy 1994). In 1995, URTI was the most frequent reason for seeking ambulatory care in the United States, resulting in more than 37 million visits to physician practitioners and emergency departments (Gonzales 2001a). It is also the most common reason for absence from work in the United States. Losses in income for employed persons, costs to employers with time lost from work and costs of medical treatment amounted to USD 112 billion in 1997 (Birnbaum 2002).

Laryngeal inflammation may be due to many causes, such as viral infection, acid reflux, voice abuse, toxic inhalation, caustic ingestion, irritation from purulent sinus drainage, hypersensitivity reactions, immune disorders or from coughing due to any cause (Koufman 1996).

Acute laryngitis is one of the most common pathologies identified in the larynx and can be defined as an inflammation of the larynx and vocal fold mucosa, lasting less than three weeks. Episodes are usually self limiting and are influenced by weather conditions (Danielides 2002; Vaughan 1982). Symptoms of acute laryngitis include a lowering of the normal pitch of the voice and hoarseness, which usually persist for three to eight days. Patients with laryngitis may also experience symptoms of an URTI, such as sore throat, odynophagia, rhinorrhoea, dyspnoea, postnasal discharge and congestion (Postma 1998; Schalen 1988; Spiegel 2000). Direct examination with a flexible nasolaryngoscope usually reveals secretions, erythema and oedema of the vocal folds.

Aetiology is not established in routine practice and the diagnosis can often be made by history alone. Unfortunately, there are no clinically useful criteria that help to distinguish between bacterial and viral infections (Vaughan 1982). Acute infectious laryngitis is usually caused by a viral infection. Respiratory viruses like parainfluenza, rhinovirus, influenza and adenovirus have been aetiologically associated with laryngitis (Higgins 1974; Postma 1998). However, bacterial pathogens such as *Moraxella catarrhalis* (*M. catarrhalis*),*Haemophilus influenzae* (*H. influenzae*) and *Streptococcus pneumoniae* (*S. pneumoniae*) have been frequently isolated from the nasopharynx in adults with acute laryngitis (Hol 1996; Schalen 1980; Schalen 1988; Verduin 2002); another related pathogen is *Chlamydia pneumoniae* (*C. pneumoniae*) (Hashiguchi 1992).

Description of the intervention

URTIs represent one of the most common causes of antimicrobial use and a frequent reason for prescribing antibiotics in ambulatory practice and primary care (Cohen 2012; Gonzales 2001a; McAvoy 1994; McCaig 1995; Steinman 2003a; WHO 2003; Wirtz 2010). In adults with acute laryngitis, treatment is usually directed toward the control of symptoms with voice rest, analgesic therapy and humidification. Macrolides, cephalosporins, a combination of penicillins with beta-lactamase inhibitors and extended-spectrum penicillins are also frequently prescribed (McGregor 1995; Steinman 2003a). Other agents such as fusafungine oro-nasal spray have been used for treating nasal and throat infections. Fusafungine has a bacteriostatic activity against most micro-organisms involved in respiratory tract infections and has anti-inflammatory properties (Lund 2004). In an observational study of the antibiotic prescribing behaviour of general practitioners in managing URTIs, 14.9% of antibiotic treatment courses were prescribed for treating laryngitis or tracheitis (Mazzaglia 1998). A retrospective analysis for a five-year period of 9.6 million physician office visits by patients with URTIs found that antibiotics were prescribed at more than 50% of visits (Sun 2006).

Reasons for over-prescribing antibiotics are varied but they often involve physicians' and patients' attitudes and expectations (Bertino 2002; Mazzaglia 1998; Steinman 2003a). A Cochrane systematic review evaluated the effectiveness of professional interventions in improving antibiotic prescriptions by healthcare providers in outpatient settings as well as the impact of these interventions on reducing the incidence of antimicrobial resistant pathogens. The authors concluded that a multi-faceted intervention, with educational interventions occurring at many levels, including repeated media campaigns, implementation of guidelines and feedback to the profession on antibiotic prescribing data and resistance, may improve antibiotic prescribing behaviour and stop the increase in the prevalence of resistant pneumococci, *H. influenzae* and other micro-organisms (Arnold 2005; Malmvall 2007). In addition, one study conducted in the United States found that antibiotic utilisation varies substantially among commercial health plans (Steinman 2009).

Why it is important to do this review

Concerns about the emergence and spread of antimicrobial resistance have been raised by the World Health Organization (WHO) (WHO 2014). The WHO 2014 report on antimicrobial resistance observed very high rates of resistance in bacteria "that cause common health-care associated and community-acquired infections in all WHO regions". The excessive use of antibiotics in ambulatory practice has contributed to the emergence and spread of antibiotic-resistant bacteria in the community, at a substantial cost to the healthcare system (Gonzales 2001a; Gonzales 2001b; Steinman 2003b). As the cost of medical treatment for laryngitis is high (Birnbaum 2002; Cohen 2012), and there is increasing concern over the resistance of common bacteria to commonly used antibiotics, there is a need to investigate the role of antibiotic drugs in acute laryngitis.

OBJECTIVES

To assess the effectiveness and safety of different antibiotic therapies in adults with acute laryngitis. A secondary objective was to report the rates of adverse events associated with these treatments.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) comparing antibiotic therapy with placebo or another antibiotic in the treatment of acute laryngitis.

Types of participants

We included adults with acute laryngitis, defined by the International Classification of Health Problems in Primary Care

(ICHPPC) as hoarseness associated with other symptoms of URTI. We excluded participants with relevant chronic underlying diseases, those displaying symptoms of laryngitis for more than three weeks (chronic laryngitis) and those receiving antibiotic therapy within the two weeks preceding diagnosis.

Types of interventions

We included trials comparing antibiotics with placebo or antibiotics of a different class for acute laryngitis.

Types of outcome measures

Primary outcomes

1. Clinical improvement
   a. Improvement in recorded voice score assessed by an expert panel at presentation and after the period of time considered in each trial (usually one or two weeks, or both). As a standard, trials used the patient's normal voice, recorded weeks later.
   b. Symptom improvement at presentation (hoarseness/ subjective voice score, pharyngitis, cough, sore throat and rhinorrhoea/nasal congestion) and after the period of time considered in each trial, as assessed by the investigators or the patient.

Secondary outcomes

1. Bacteriological findings
   a. Evaluated at the acute and follow-up visits.
2. Adverse reactions following antibiotic therapy
   a. Serious adverse events, i.e. serious enough to require withdrawal from the treatment group.
   b. Minor adverse events reported by participants and not requiring withdrawal from the treatment group (gastrointestinal side effects such as diarrhoea, dyspepsia, abdominal pain and rash).
3. Laryngoscopic findings
   a. Evaluated at the acute and follow-up visits.

Search methods for identification of studies

Electronic searches

For this 2014 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 11) (accessed 16 December 2014), which includes the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (January 2013 to November week 3, 2014), EMBASE (January 2013 to December 2014), LILACS (January 2013 to December 2014) and BIOSIS (January 2013 to December 2014).

The CENTRAL and MEDLINE search strategies are in Appendix 1. We combined the MEDLINE search with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefevbre 2011). We adapted the search strategy to search EMBASE (Appendix 2), LILACS (Appendix 3) and BIOSIS (Appendix 4). Details of earlier searches are in Appendix 5.

We imposed no language or publication restrictions.

Searching other resources

We employed other strategies including the searching of references of review articles and books related to infections of the respiratory tract, and handsearches of journals such as *Journal of Infectious Diseases*,*Clinical Infectious Diseases*,*Journal of Antimicrobial Chemotherapy*,*Head and Neck*,*Otorhinolaryngology*,*Annals of Otology Rhinology and Laryngology* and*Scandinavian Journal of Infectious Diseases* (for the 2008 update).

We searched grey literature such as conference abstracts/ proceedings, published lists of theses and dissertations worldwide (dissertation abstract database), letters, government documents (CDC database) and other literature outside of the main journal literature, where possible (McAuley 2000).

We contacted some pharmaceutical companies to obtain unpublished trial data. We contacted leading researchers involved in the field by e-mail to obtain information on additional published and unpublished data and trials (for the 2008 update).

We also consulted local and international experts in the field and searched databases of ongoing trials registers such as the International Clinical Trials Registry Platform (ICTRP) search portal (http://www.who.int/trialsearch/Default.aspx) using the following terms: acute laryngitis.

Data collection and analysis

Selection of studies

Two review authors (LR, AC) independently retrieved the articles and assessed their eligibility from the title and abstracts.

Data extraction and management

Two review authors (LR, AC) independently assessed the full text of all studies identified as possibly relevant. The review authors were not blinded to the origin or conclusions of the article during eligibility assessment, data extraction or quality assessment (Berlin 1997).

Assessment of risk of bias in included studies

Two review authors (LR, AC) independently assessed the risk of bias for each study as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion. The possible sources of bias described below are considered and reflected in the 'Risk of bias' table for each included study. Whenever possible we included additional information with a clarifying comment or a quoted sentence taken directly from the original article.

We assessed the following domains as low risk of bias, unclear or high risk of bias:

1. Generation of allocation sequence
2. Allocation concealment
3. Blinding (of participants, personnel and outcome assessors)
4. Incomplete outcome data
5. Selective reporting
6. Other sources

(1) Generation of allocation sequence (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as follows.

- Low risk (any truly random process, e.g. random number table; computer random number generator).
- High risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number).
- Unclear risk, if the trial was described as randomised, but the method used for the allocation sequence generation was not described.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as follows.

- Low risk (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes).
- High risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth).
- Unclear risk, if the trial was described as randomised, but the method used to conceal the allocation was not described.

(3) Blinding or masking (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We judged studies at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as follows.

- Low risk, high risk or unclear for participants.
- Low risk, high risk or unclear for personnel.
- Low risk, high risk or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, drop-outs, protocol deviations)

We assessed the methods as follows.

- Low risk (any one of the following): no missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
- High risk (any one of the following): reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardised difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
- Unclear risk (any one of the following): insufficient reporting of attrition/exclusions to permit judgement of 'low risk' or 'high risk' (e.g. number randomised not stated, no reasons for missing data provided); the study did not address this outcome.

(5) Selective reporting bias (reporting bias due to selective outcome reporting)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as follows.

- Low risk (any one of the following): the study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way or the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
- High risk (any one of the following): not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
- Unclear risk: insufficient information to permit judgement of 'low risk' or 'high risk'.

(6) Free of other bias (bias due to problems not covered elsewhere in the table)

We described for each included study any important concerns we have about other possible sources of bias (baseline imbalance, sponsorship bias, confirmation bias, bias of the presentation data, etc.)

- Low risk of bias: the trial appears to be free of other components that could put it at risk of bias.
- Unclear risk: the trial may or may not be free of other components that could put it at risk of bias.

- High risk of bias: there are other factors in the trial that could put it at risk of bias, e.g. no sample size calculation made, academic fraud, industry involvement or extreme baseline imbalance.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors independently carried out data extraction using a previously designed form to ensure validity. Discrepancies were resolved by an open discussion between all review authors. The differences in the study participants, interventions and outcomes among the included trials are presented in the Characteristics of included studies table.

We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to assess the quality of the body of evidence as related to the following outcomes (Guyatt 2013).

- Clinical cure rates

We used Review Manager 5.3 to create 'Summary of findings' tables (RevMan 2014). We produced a summary of the intervention effect and a measure of quality for each of the above outcomes using the GRADE approach. The GRADE approach is based on five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias), which are used to assess the quality of the body of evidence for each outcome. Evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias (Guyatt 2013).

Measures of treatment effect

We assessed the measurement of the intervention effect for dichotomous outcomes using the risk ratio (RR). We assessed the measurement of the intervention effect for continuous outcomes using the mean difference (MD).

Unit of analysis issues

We found no studies with non-standard designs, such as cross-over trials and cluster-randomised trials.

Dealing with missing data

In future updates, we will address missing data for dichotomous outcomes by an intention-to-treat (ITT) analysis. We will consider the potential impact of these missing data in the interpretation of the results of the review when necessary.

Assessment of heterogeneity

In future updates, we will assess heterogeneity using the I^2 statistic. We will interpret the I^2 statistic according to the following thresholds: less than 25% will be considered as low level heterogeneity; 25% to 50% as moderate level; and higher than 50% as high level heterogeneity (Higgins 2011).

We will explore potential sources of heterogeneity by means of a subgroup analysis when possible.

Assessment of reporting biases

For future updates, if there are 10 or more studies in the meta-analysis we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually and use formal tests for funnel plot asymmetry (Higgins 2011).

Data synthesis

For future updates, we will use fixed-effect meta-analysis for combining data where it is reasonable to assume that studies are estimating the same underlying treatment effect, i.e. where trials are examining the same intervention and the trials' populations and methods are judged sufficiently similar. We will use a random-effects meta-analysis if clinical heterogeneity is sufficient to expect that the underlying treatment effects differ between trials, or if substantial statistical heterogeneity is detected, to produce an overall summary if an average treatment effect across trials is considered clinically meaningful. We will treat the random-effects summary as the average range of possible treatment effects. If we use random-effects analyses, we will present the results as the average treatment effect with its 95% confidence interval, and the estimates of the T^2 and I^2 statistic (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

For future updates, we will perform subgroup analysis in order to investigate heterogeneity by studying the factors that contribute to clinical heterogeneity. We will perform subgroup analyses according to gender, age and different doses of antibiotics administered.

Sensitivity analysis

For future updates, we plan to carry out a sensitivity analyses according to 'Risk of bias' assessment (Higgins 2011).

RESULTS

Description of studies

Results of the search

This is an updated version of the original review published in Issue 1, 2005 of *The Cochrane Library* (Reveiz 2005). From the results of the extensive literature searches, we initially identified 3610 citations as potentially relevant. We performed updated searches from June 2004 to December 2006, from December 2006 to November 2008, from October 2008 to February 2011, from January 2011 to January 2013 and from January 2013 to December 2014, resulting in 263 additional citations. Manual culling reduced this to four reports of possibly eligible trials. Only three trials fulfilled the criteria for inclusion (Rafalskiy 2012; Schalén 1985; Schalén 1993), and we excluded a duplicated trial (Schalén 1992). Schalén 1985 and Schalén 1993 were conducted by the same group of researchers in Sweden and Rafalskiy 2012 was conducted in Russia. Additional searches conducted to identify other relevant studies or unpublished data did not uncover any new trials. Although we identified 32 trials in the ICTRP database (December 2014), no ongoing trials complied with the inclusion criteria.

Included studies

In a study of penicillin V in acute laryngitis in adults (Schalén 1985), 100 participants over 18 years of age were examined and recruited at the otolaryngology department of the University of Lund, Sweden to receive either penicillin V (800 mg two times a day for five days) or an identical placebo. No participants were reported to have dropped out or as having been lost to follow-up. Exclusion criteria included participants with relevant underlying diseases such as chronic bronchitis, pregnancy, antibiotic treatment within the preceding two weeks and a history of penicillin allergy.

The trial measured the symptoms of hoarseness (subjective voice score), cough, rhinorrhoea and nasal congestion using self reported daily records collected in a questionnaire. At the acute visit, indirect laryngoscopy revealed laryngeal signs of inflammation in 97% of the cases (not conclusive in three cases due to intense throat reflexes)). A voice recording of standardised text was obtained for each patient at the first visit and subsequently at re-examinations at five to seven days, 10 to 14 days, and two to six months following the acute episode. The four recordings from each patient were presented in random order to four experienced voice specialists. The voice samples were evaluated with regards to 10 different qualities of voice (no further description of the quality of voice was provided). Each quality was evaluated individually by the members of the group using a quantitative score (0 = normal, 1 = slight aberration, 2 = abnormal) and the sum of each result was used to obtain an average score for the penicillin V and placebo groups. Microbiological specimens were collected from the nasopharynx and throat at the initial visit and one and two weeks later.

The second trial investigated erythromycin for the treatment of acute laryngitis in adults (Schalén 1993). One hundred and six consecutive participants were recruited at the otolaryngology department of the University of Lund, Sweden, and 90 completed the double-blind trial. Six participants failed to keep scheduled appointments and one presented with an exanthema on the second day of antibiotic treatment. Participants lost to follow-up were not included in the analysis. Participants were randomised to receive either erythromycin ethylsuccinate (taken orally twice daily for five days) or placebo in identical tablets. The inclusion and exclusion criteria, outcomes and follow-up were the same as the first trial. However, a different voice score (0 = normal, 1 = slight aberration, 2 = moderate aberration, 3 = severe aberration) and 12 voice qualities (rough voice, diplophonia, breathiness, vocal fry, episodes of aphonia, registered abnormalities, registered breaks, sonority, hyperfunction and hypofunction, and high or low pitch) were used in the second trial.

The trial from Russia was reported as an abstract at the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); a full report was not available from a peer-reviewed journal (Rafalskiy 2012), and although efforts were made to contact the trial authors, we obtained no further information. The study included 145 adult patients with symptoms of acute laryngitis. However, no further eligibility criteria were provided. Participants were randomised to three groups of treatment: Group 1: seven-day course of fusafungine (Bioparox®, Servier) (six times a day by inhalations); Group 2: seven-day course of fusafungine (Bioparox®, Servier) (six times a day by inhalations) plus clarithromycin (Clacid®, Abbott) (250 mg twice a day for seven days); and Group 3: no treatment. Clinical cure rates were measured at days 5 ± 1, 8 ± 1 and 28 ± 2.

Excluded studies

We excluded only one study from the review (see Characteristics of excluded studies).

Risk of bias in included studies

We considered studies to have moderate to high risk of bias (see Risk of bias in included studies, Figure 1 and Figure 2).

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

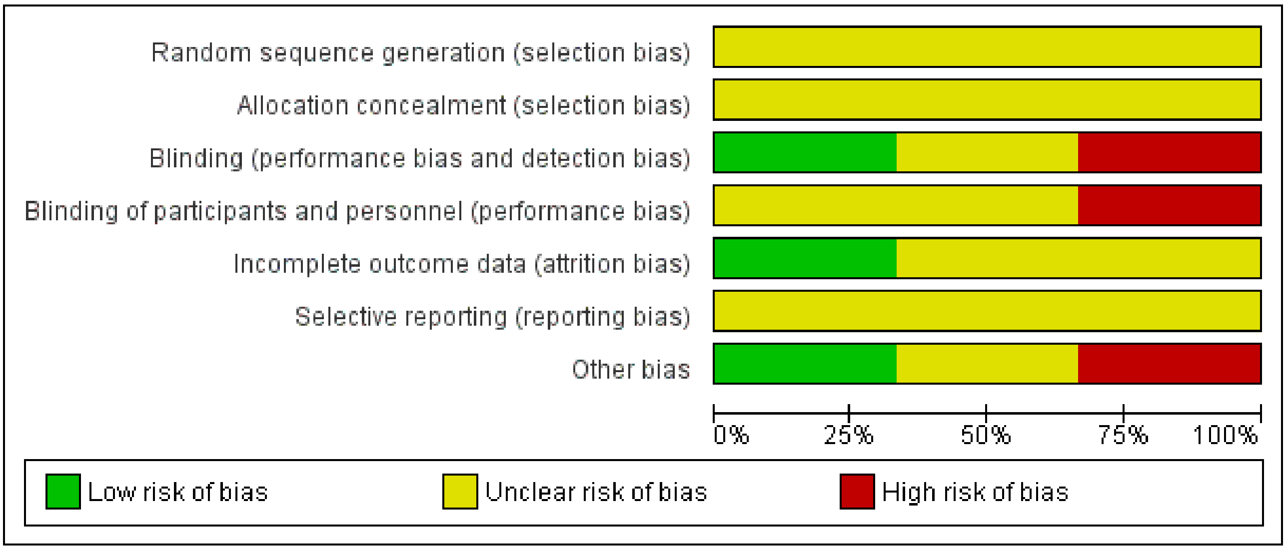
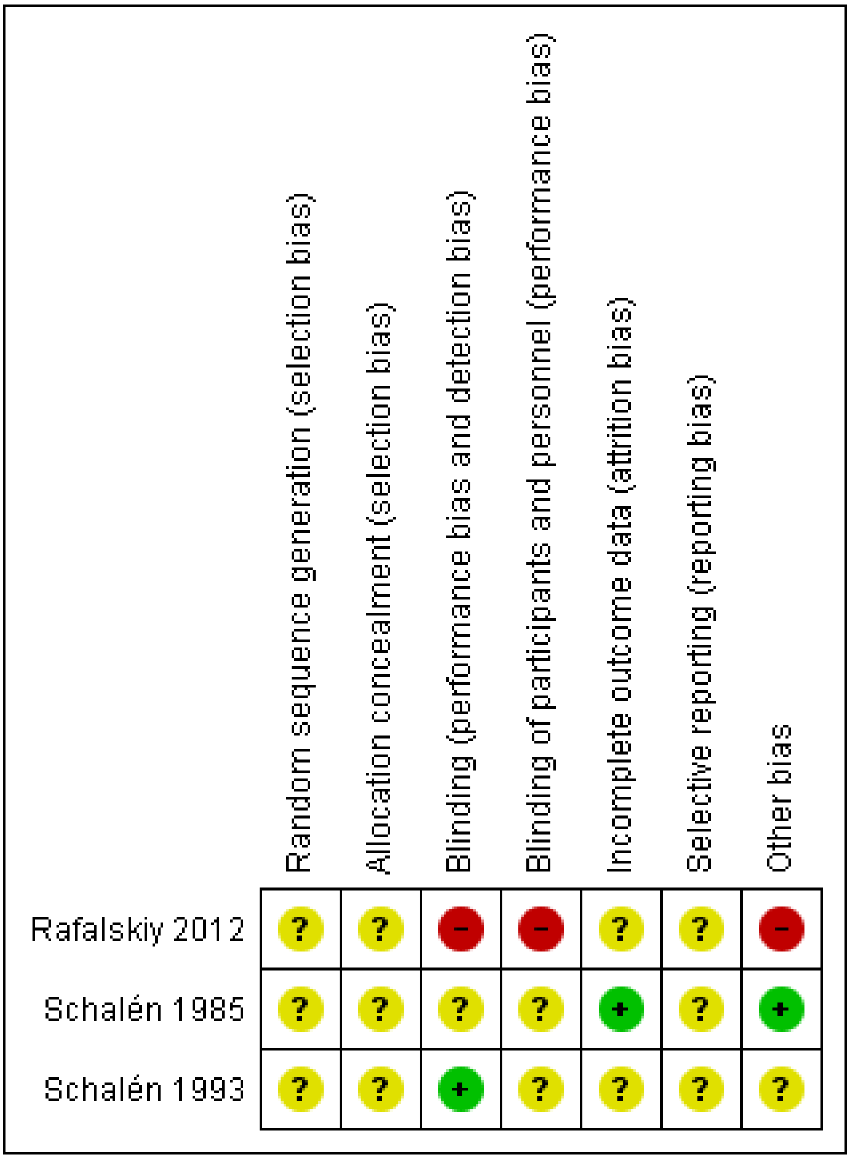


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study



In the penicillin V study (Schalén 1985), methods to generate the sequence of randomisation and allocation concealment were not reported. Furthermore, no description of the sample size or power calculation was recorded. Both the participants and treating physicians were blinded. However, the characteristics of this blinding were not described. No drop-outs or withdrawals were reported.

Information was given regarding baseline characteristics including gender, age, voice demand or abuse, smoker condition and previous laryngitis (three or more episodes during the preceding five years) making it easy to ascertain that the groups were sufficiently similar at the start of the trial. There were no statistically significant differences between the two groups in symptoms and clinical findings at the acute visits (in terms of preceding URTI, presence of rhinitis, cough and sore throat, abnormal findings like redness and oedema in the larynx, pharynx and epipharynx, mean voice score and bacterial pathogen isolated from the nasopharynx).

The mean interval between the start of vocal symptoms and the first evaluation was 3.6 days. However, the interval was longer for participants receiving antibiotics (3.8 ± 3.3) compared to the placebo (3.4 ± 3.0). All data were evaluated using a cross-tabulated Chi^2 test and a probability level of 0.01 was considered significant.

The erythromycin study publication, Schalén 1993, stated that the trial was randomised and participants and physicians were blinded by using identical placebo tablets. A power calculation and intention-to-treat (ITT) analysis were not reported. Seven of 106 participants dropped out or withdrew from the study for specific reasons and were not accounted for in the trial analysis. Baseline characteristics of the participants appeared to be broadly similar between groups and included the same variables as the penicillin V study. As they were not described, we calculated P values for any differences in the population characteristics and the symptoms and signs at presentation and found no significant difference between the two groups.

The erythromycin group had a significantly higher proportion of bacterial pathogens and *M. catarrhalis* was isolated from the nasopharynx in this group (P value = 0.045 and P value = 0.012, Fisher's exact test), respectively. The mean interval between the start of vocal symptoms and the first evaluation was not reported. Non-parametric tests were used for statistical analysis. Fisher's exact probability test was used to compare bacterial elimination rates between the two groups and the Mann-Whitney U test with adjusted z was used for all other comparisons. A probability level of 5% was considered significant.

In the open trial from Russia the methods used to generate the sequence of randomisation and allocation concealment were not reported (Rafalskiy 2012). Information on relevant prespecified outcomes and baseline characteristics was not provided.

Allocation

We judged the methods of randomisation and allocation concealment to be unclear in all RCTs.

Blinding

Both trials from Sweden were reported as "double blind". However, it was unclear if the methods to ensure blinding were effective. There was insufficient information to permit judgement of 'low risk' or 'high risk' on blinding of participants and personnel and blinding of the outcome assessment. The trial from Russia had an open design and we judged it as having high risk of bias (Rafalskiy 2012).

Incomplete outcome data

One trial had no drop-outs and we judged it as having low risk of bias (Schalén 1985). In another trial, 15% of participants were lost to follow-up and we judged it as having unclear risk of bias (Schalén 1993). No participants were reported as having been lost to follow-up at days five and eight in the Rafalskiy 2012 trial. However, 72% of participants did not provide data at day 28.

Selective reporting

We judged both Swedish trials as having unclear risk of bias. The Rafalskiy 2012 trial did not provide detailed information on the improvement in recorded voice score, specific adverse events, or bacteriological or laryngoscopic findings and we judged it as having high risk of bias.

Other potential sources of bias

Other potential sources of bias are summarised in the 'Risk of bias' tables. No report on coadjuvant medication was provided in the Rafalskiy 2012 trial.

Effects of interventions

See: **Summary of findings for the main comparison**; **Summary of findings 2**; **Summary of findings 3**

Primary outcomes

1. Clinical improvement

A. Improvement in recorded voice score

In the penicillin V trial the mean objective voice scores at the first visit and at re-examination after one and two weeks, as well as at follow-up after two to six months, did not differ significantly between the penicillin V and the placebo groups (Schalén 1985). Significant improvement was reported in the severity of reported vocal symptoms, nasal congestion/rhinorrhoea, throat symptoms, cough and laryngeal abnormalities evaluated by indirect laryngoscopy at the follow-up examinations in the control and intervention groups, as judged by the participants. Significant improvement measured by higher mean voice scores was found at the acute visits among participants with *M. catarrhalis*, *H. influenzae* or *S. pneumoniae* (26 ± 8) isolated from the nasopharynx, compared to results obtained for those with negative cultures (20 ± 10) (P value < 0.05). However, the subjective voice scores at the acute visits did not differ between the participants harbouring the three mentioned pathogen isolates and those without the organisms. This study used parametric measures. Data were not available to calculate estimates.

In the erythromycin trial the mean objective voice scores at the first visit, at re-examination after one and two weeks, and at follow-up after two to six months, did not differ significantly between control and intervention groups (Schalén 1993). Thirty randomly selected voice samples recorded at presentation were evaluated and the Kendall coefficient of concordance between listeners for the voice qualities ranged from 0.45 to 0.91. (The Kendall's coefficient of concordance is a measure of the agreement among several judges who are assessing a given set of objects). After one week, the mean scores were clearly reduced and the voice profiles were essentially normalised in both groups.

B. Symptom improvement at presentation

In the Rafalskiy 2012 trial, the authors reported no significant differences when comparing fusafungine versus fusafungine plus clarithromycin at days 5 ± 1, 8 ± 1 and 28 ± 2 (Analysis 1.1; Analysis 1.2; Analysis 1.3). However, significant differences were reported in the rates of clinical cure at day 5 ± 1 favouring fusafungine (one trial; 93 participants; RR 1.50, 95% CI 1.02 to 2.20; Analysis 2.1) and fusafungine plus clarithromycin (one trial, 97 participants; RR 1.47, 95% CI 1.00 to 2.16; Analysis 3.1) when compared to no treatment. Additionally, no significant differences were found at days 8 ± 1 and 28 ± 2 in the rates of clinical cure for both comparison (Analysis 2.2; Analysis 2.3; Analysis 3.2; Analysis 3.3) or in the rate of adverse events when comparing fusafungine versus fusafungine plus clarithromycin (Analysis 1.4).

There were no significant differences in the clinical examinations after one and two weeks in the presence of resolution of laryngitis (one trial, 99 participants; risk ratio (RR) 1.10, 95% confidence interval (CI) 0.76 to 1.59 (Analysis 4.1) and RR 0.81, 95% CI 0.44 to 1.49 (Analysis 4.2), respectively). In addition, although there was a significant improvements in the rate of patients having voice disturbance at week one when comparing erythromycin and placebo groups as judged by the participants (one trial, 99 participants, RR 0.64, 95% CI 0.46 to 0.90 (Analysis 4.5) no significant difference was found at week two (RR 0.56, 95% CI 0.28 to 1.14 (Analysis 4.6)). However, comparing the erythromycin and placebo groups significant improvements were found in the severity of reported vocal symptoms as judged by the participants.

While significantly fewer complaints of cough were reported by the erythromycin group compared to the placebo group at week two (one trial, 99 participants; RR 0.38, 95% CI 0.15 to 0.97; Analysis 4.8), no difference was found at week one (Analysis 4.7). The trialists also compared signs pharyngitis and rhinitis, evaluated by mirror endoscopy or direct inspection, and found no statistical differences between the two groups.

We did not aggregate results from the trials as there was significant heterogeneity between them, with different drugs and definitions of some outcomes.

Secondary outcomes

1. Bacteriological findings

In the penicillin V trial *M. catarrhalis*,*H. influenzae* and *S. pneumoniae* were isolated from 50%, 15% and 1% of the participants respectively, at the first evaluation (Schalén 1985). The isolation rates of each of the mentioned pathogens at the acute and follow-up visits did not differ significantly between the two intervention groups.

In the erythromycin trial *M. catarrhalis* was isolated from the nasopharynx in 50% of participants, *H. influenzae* in 20% of participants and *S. pneumoniae* in 5% of participants at the acute visit (Schalén 1993). After one week, *M. catarrhalis* was eliminated in 83% of the participants in the erythromycin group as compared with 32% in the placebo group (one trial, 49 participants; RR 2.64, 95% CI 1.34 to 5.21; Analysis 4.3). However, there was no difference between the two groups in the recovery rate of *M. catarrhalis* at two weeks (Analysis 4.4).

2. Adverse reactions following antibiotic therapy

A. Serious adverse events

No deaths were reported in either the penicillin V trial (Schalén 1985) or the erythromycin study (Schalén 1993). No adverse drug reactions were reported in the penicillin V trial (Schalén 1985), although it was unclear which potential toxic effects were monitored for.

B. Minor adverse events reported by participants

Only one patient was reported to present with an exanthema, on the second day of erythromycin treatment. The frequency of adverse events was not significantly different between the fusafungine versus fusafungine plus clarithromycin groups (one trial; 100 participants; RR 0.81, 95% CI 0.19 to 3.45; Analysis 1.4) (Rafalskiy 2012).

3. Laryngoscopic findings

None of the studies reported the outcome laryngoscopic findings.

DISCUSSION

Summary of main results

Overall, the available evidence is of poor quality and antibiotics did not improve objective outcome measures in patients with acute laryngitis. Erythromycin could reduce voice disturbance at one week and cough at two weeks when measured subjectively. In the more recently included trial, fusafungine or fusafungine plus clarithromycin were more effective than no treatment in patients with acute laryngitis at day five, but no significant differences were found at days eight and 28 (Rafalskiy 2012). However, no significant differences were found when adding clarithromycin to fusafungine. In addition, we judged this study, which was presented as an abstract in a conference, as having high risk of bias for many domains of the 'Risk of bias' tool. We consider that these findings are not sufficient to justify the use of antibiotics in clinical practice. Treating laryngitis with conservative measures in the first instance is reasonable as it remains unclear that antibiotics are worthy and beneficial to individuals or populations, particularly in the context of antimicrobial resistance (WHO 2014).

Benefits of treatment

The effectiveness of antibiotic treatment for the common cold and for sore throat is covered in other Cochrane Reviews (Arroll 2013; Spinks 2013). Trials identified in those reviews included some participants with symptoms of acute laryngitis; conditions that affect the upper respiratory tract are not a single entity. Acute laryngitis may result from direct infection of the larynx, from irritation of the larynx due to coughing or from contact with infected secretions. Hence the supposition that acute laryngitis, along with other conditions that affect the upper respiratory tract, may not be related to one particular cause. As mentioned by Arroll et al, the review authors had to accept the clinical judgement of the trialists as to which participants were included in their upper respiratory tract infection (URTI) clinical trials (Arroll 2013).

Erythromycin is apparently effective at reducing voice disturbances as measured by participants after one week and cough after two weeks. The authors considered that these findings suggested the usefulness of antibiotics in a special subgroup of people for whom voice function was essential to their professional or social activities, but their use appeared to be discretionary rather than mandatory. We calculated a risk ratio (RR) of 0.64 (95% confidence interval (CI) 0.46 to 0.90, P value = 0.034) with a number needed to treat for an additional beneficial outcome (NNTB) of 3.76 (95% CI 2.27 to 13.52; P value = 0.01) for the subjective voice scores at one week, considering total improvement as score '0' and partial or no improvement as the sum of scores 1, 2 and 3; for cough after two weeks the RR was 0.38 (95% CI 0.15 to 1, P value = 0.058). Conversely, a lack of improvement in subjective measures was found with the use of penicillin V (Schalén 1985).

In the Rafalskiy 2012 trial, adding clarithromycin to fusafungine did not show any significant difference in the rates of cured patients. When comparing fusafungine to no treatment at day 5 ± 1, we calculated a NNTB of 4.5 for the clinical cure outcome.

Acute laryngitis is a self limiting condition that usually varies in duration from three to eight days. Considering that the time taken from the start of hoarseness to the visit reported in the penicillin V trial was 3.6 (± 3.2) days (Schalén 1985), most of the first re-examinations would have been done five to seven days later, when symptoms were likely to have disappeared. Outcomes such as reduction of illness time and absolute reduction averaged over the whole illness were not estimated in the present trials. These clinically important outcomes and other outcomes, such as re-attendance or time off school or work, are probably at least as important as those that were used. It is important to state that the use of the voice score attempts to qualify different signs in a quantitative manner. This implies some subjectivity in assessing each score. Furthermore, the trial authors assumed that any difference from zero to one, or from one to two, was equally relevant, and the 10 (or 12) signs analysed were also considered equally important (Altman 1999).

The Swedish trials only included people with laryngitis who were admitted to the ear, nose and throat department, which may have led to selection bias that favoured participants with severe symptoms. People with this condition will often not go to hospital or consult a primary care practitioner (Cherry 2003; McAvoy 1994). Another concern was information not collected by the trial authors, such as the concomitant use of other medications that may alter the course of illness, for example, decongestants, heated or humidified air, or voice rest, etc.

Adverse effects of treatment

Reporting on the adverse effects of antibiotic use was irregular. Other studies have described rare but severe adverse reactions, for example, hepatotoxicity, transient deafness and allergic reactions. Gastrointestinal symptoms represented the most frequent disturbance, occurring in 15% to 20% of participants on erythromycin. A significant number of drug interactions have also been reported (FDA 2004; Periti 1993).

Natural history and microbiological findings

Natural history and microbiological findings also support the non-use of antimicrobials. Almost 20 years ago bacterial pathogens such as *M. catarrhalis* and *H. influenzae* were implicated in the genesis of upper respiratory tract infection (URTI) and acute laryngitis. This conclusion was based on studies that confirmed that carriage of these pathogens is an uncommon feature in healthy adults (DiGiovanni 1987; Ejlertsen 1994; Schalen 1980). The involvement of the larynx in a viral infection could, in a proportion of patients, lead to bacterial superinfection with extensions to the upper and lower respiratory tract.

The high nasopharyngeal isolation rates of *M. catarrhalis* (50% in both studies) and *H. influenzae* (15% in the penicillin V trial and 20% in the erythromycin trial) were apparently consistent with the use of antibiotics for this condition. However, after one week the voice profiles appeared to be essentially normalised in both antibiotic and placebo groups in both trials; no relevant differences were found in clinical symptoms assessed by the participants apart from the above described. These findings support the conclusion that the disorder is generally self limiting, and the majority of participants in the studies may have been suffering from viral URTIs.

Isolates of *M. catarrhalis*, as reported by Schalén et al in both trials (Schalén 1985; Schalén 1993), were obtained from swabs placed in haematin agar tubes and inoculated onto haematin agar plates in 6% CO^2 atmosphere as well as onto blood agar plates incubated anaerobically. *M. catarrhalis*, considered by the authors to be the principal bacterial pathogen related to acute laryngitis, was confirmed by fermentation reactions and by testing for species-specific protein antigen. If no growth was found, the swabs kept in the haematin agar tubes were streaked and incubated as above.

Over the years the following criteria have been used to clearly identify *M. catarrhalis* from other bacterial species: gram stain (Verduin 2002); colony morphology; lack of pigmentation of the colony on blood agar; oxidase production; DNAase production; failure to produce acid from glucose, sucrose, fructose, lactose and maltose; growth at 22°C on nutrient agar; failure to grow on modified Thayer-Martin medium; and, finally, reduction of nitrite and nitrate. Currently, the identity of this pathogen is best confirmed by positive reactions in at least three of the following tests, since none are 100% sensitive or specific by themselves: positive reaction for DNAase production, reduction of nitrate and nitrite and tributyrin hydrolysis (Catlin 1990). Furthermore, polymerase chain reaction (PCR) tests are currently considered an unequalled diagnostic assay (Greiner 2003; Post 1995; Post 1996). Modern tests show that the methods used in the present trials to identify *M. catarrhalis* may have introduced some misclassification in the percentage of isolates of this pathogen in participants with acute laryngitis.

By the years 1980 and 1990, the presence of B-lactamase in isolates of *M. catarrhalis* from the United States was 75% and 80% respectively. By 1990, B-lactamase was in over 90% of isolates from England and Scotland; and, by 2003, in 87.4% of isolates from China (Fung 1991; Jorgensen 1990; Wallace 1990; Wang 2003). In a study conducted in the United States, most isolates of *M. catarrhalis* were resistant to amoxicillin, cefaclor, cefprozil and trimethoprim/sulfamethoxazole; among *H. influenzae* isolates, 28.6% were B-lactamase positive (Jacobs 2004). In the present penicillin trial, 18% of *M. catarrhalis* isolated at the acute visit produced B-lactamase.

Overall completeness and applicability of evidence

There were only three randomised controlled trials (RCTs) in this review and the data are incomplete for a number of clinically important outcomes. In addition there was no opportunity to pool data. The applicability of the evidence outside the research setting is reasonable as these studies were conducted in clinical settings that were quite similar. The comparisons in the review are commonly undertaken and not difficult to apply. Two RCTs were conducted in Sweden and another one in Russia.

Quality of the evidence

The quality of the evidence was very low for all outcomes, as per the GRADE approach. The main reasons for downgrading the quality of the evidence were limitations in study design or execution (risk of bias), imprecision and inconsistency of results. The review included three small trials, which we judged as having moderate to high risk of bias, mainly because allocation concealment methods were not adequately reported, no blinding was performed, outcomes measure were not adequately defined and concomitant treatments were unclear in some trials. Another limitation was incomplete outcome reporting (e.g. continuous outcomes failed to provide standard deviations in several RCTs) and no reporting of baseline characteristics. In two of the studies, diagnosis was made through indirect laryngoscopy (Schalén 1985; Schalén 1993). A more accurate diagnostic approach would have required a more specialised examination. These RCTs assessed different interventions resulting in very limited opportunities to pool useful data. Publication bias could not be evaluated, given the small number of trials identified for each comparison.

Potential biases in the review process

We have produced updated coverage of RCTs of antibiotics for laryngitis in adults by summarising the best available evidence using quantitative methods. We endeavoured to provide information to help clinicians and stakeholders choose the most appropriate treatment. We searched several sources to identify RCTs. However, we cannot be sure that all available RCTs were identified. We included a new trial published only as a conference abstract and the results of this study need to be verified by publication in a peer-reviewed journal. Although acute laryngitis is often diagnosed using clinical criteria, laryngoscopic findings are needed for a clear diagnosis. The RCTs included in this review did not use more specialised examination of the larynx.

Agreements and disagreements with other studies or reviews

Acute laryngitis often involves rhino-pharyngo-laryngitis or rhinosinubronchitis with involvement of the larynx. A Cochrane Review assessing the effect of antibiotics in adults with clinically diagnosed rhinosinusitis in primary care settings found that although antibiotics can shorten the time to cure (number needed to treat to benefit (NNTB) 18 (95% CI 10 to 115), significantly more participants who received antibiotics experienced adverse events (number needed to treat to harm (NNTH) 8 (95% CI 6 to 13) (Lemiengre 2012). The authors concluded that there is no place for antibiotics in patients with clinically diagnosed, uncomplicated acute rhinosinusitis.

AUTHORS' CONCLUSIONS

Implications for practice

Definitive recommendations cannot be made since evidence is only available from three randomised controlled trials (RCTs). Antibiotics appear to have no benefit in the treatment of acute laryngitis. Erythromycin may reduce voice disturbance at one week and cough at two weeks, measured subjectively, and fusafungine may improve the rates of cured patients at day five (it is unclear how this was measured), however we consider that these outcomes are not relevant in clinical practice. In addition, acute laryngitis requires laryngoscopic findings for a clear diagnosis as hoarseness by itself is not the sole criterion for the assessment of a disease. Overall, there is no clear benefit for the primary outcome, which is objective assessment of voice quality, but some improvements are seen in subjective measures (i.e. cough, hoarseness of voice) that could be important to patients. However, we consider that these modest benefits from antibiotics may not outweigh their cost, adverse effects or negative consequences for antibiotic resistance patterns. The implications for practice are that prescribing antibiotics should not be done in the first instance as they will not objectively improve symptoms.

Implications for research

Definitive recommendations cannot be made based on the evidence provided by these low-quality trials; antibiotics may reduce voice disturbance and cough, and may increase cure rates. There is a need for high-quality trials to find out if these effects are real. Future research should address the limitations of previous trial methodologies (e.g. a more accurate diagnosis/case definition using direct laryngoscopy etc.) and adequately evaluate objective clinical outcomes. Study designs should be better controlled for risk of bias and confounders (e.g. allocation concealment, concomitant therapies etc.). Additionally, the potential treatment effect may have been attenuated by the inclusion of participants with non-infective bacterial causes of laryngitis; future research could also explore better ways to identify and treat those patients.

ACKNOWLEDGEMENTS

Liz Dooley and Sarah Thorning from the Cochrane Acute Respiratory Infections Group for their assistance. We also wish to thank the following people for commenting on the 2007 draft: Chanpen Choprapawon, Rob Ware and Abigail Fraser. We acknowledge Edgar Ospina, Carlos Granados and Johanna Osorio for their contributions in previous publications of this review. Finally we thank the following people for commenting on this 2014 updated review: Liz Whamond, David Barnes, Robert Ware and Hans van der Wouden.

REFERENCES

References to studies included in this review

Rafalskiy 2012 *{published data only}*

Rafalskiy VV, Gurevitch AS, Otvagin IV, Dovgan EVA. Randomized comparative study of 7-days courses of fuzafungine vs. fuzafungine and clarithromycin in patients with acute laryngitis. 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) of the American Society for Microbiology. Available at: http://www.icaaconline.com/php/icaac2013abstracts/data/papers/2012/L1/2012_L1-299.htm (accessed February 3, 2015), 2012; Vol. 52:L1299.

Schalén 1985 *{published data only}*

Schalén L, Christensen P, Eliasson I, Fex S, Kamme C, Schalen C. Inefficacy of penicillin V in acute laryngitis in adults. Evaluation from results of double-blind study. *Annals of Otology, Rhinology, and Laryngology* 1985;**94**(1 Pt 1):14-7.

Schalén 1993 *{published data only}*

Schalén L, Eliasson I, Kamme C, Schalen C. Erythromycin in acute laryngitis in adults. *Annals of Otology, Rhinology, and Laryngology* 1993;**102**(3 Pt 1):209-14.

References to studies excluded from this review

Schalén 1992 *{published data only}*

Schalén L, Eliasson I, Fex S, Kamme C, Schalen C. Acute laryngitis in adults: results of erythromycin treatment. *Acta Oto-Laryngologica. Supplement* 1992;**492**:55-7.

Additional references

Altman 1999

Altman DG. Types of data. In: Altman DG editor(s). Practical Statistics for Medical Research. Eighth. Chapman & Hall/CRC, 1999:10-18.

Arnold 2005

Arnold SR, Straus SE. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database of Systematic Reviews* 2005, Issue 4. [DOI: 10.1002/14651858.CD003539.pub2]

Arroll 2013

Arroll B, Kenealy T. Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Database of Systematic Reviews* 2013, Issue 6. [DOI: 10.1002/14651858.CD000247.pub3]

Berlin 1997

Berlin J. Does blinding readers affect the results of meta-analysis? University of Pennsylvania Meta-analysis Blinding Study Group. *Lancet* 1997;**350**:185-6.

Bertino 2002

Bertino JS. Cost burden of viral respiratory infections: issues for formulary decision makers. *American Journal of Medicine* 2002;**112**(Suppl 6A):42-9.

Birnbaum 2002

Birnbaum HG, Morley M, Greenberg PE, Colice GL. Economic burden of respiratory infections in an employed population. *Chest* 2002;**122**(2):603-11.

Castro 1997

Castro AA, Clark OAC, Atallah A. Optimal search strategy for clinical trials in the Latin American and Caribbean Health Science Literature Database (LILACS). *São Paulo Medical Journal* 1997;**115**:1423-6.

Catlin 1990

Catlin BW. Branhamella catarrhalis: an organism gaining respect as a pathogen. *Clinical Microbiology Reviews* 1990;**3**:293-320.

Cherry 2003

Cherry DK, Burt CW, Woodwell DA. National Ambulatory Medical Care Survey: 2001 summary. Advance Data. http://www.cdc.gov/nchs/data/ad/ad338.pdf (accessed 24 September 2003) 2003; Vol. 337:1-44.

Cohen 2012

Cohen SM, Kim J, Roy N, Asche C, Courey M. Direct health care costs of laryngeal diseases and disorders. *Laryngoscope* 2012;**122**(7):1582-8.

Danielides 2002

Danielides V, Nousia CS, Patrikakos G, Bartzokas A, Lolis CJ, Milionis HJ, et al. Effect of meteorological parameters on acute laryngitis in adults. *Acta Oto-Laryngologica* 2002;**122**(6):655-60.

DiGiovanni 1987

DiGiovanni C, Riley TV, Hoyne GF, Yeo R, Cooksey P. Respiratory tract infections due to Branhamella catarrhalis: epidemiological data from Western Australia. *Epidemiology and Infection* 1987;**99**:445-53.

Ejlertsen 1994

Ejlertsen T, Thisted E, Ebbesen F, Olesen B, Renneberg J. Branhamella catarrhalis in children and adults. A study of prevalence, time of colonisation, and association with upper and lower respiratory tract infections. *Journal of Infection* 1994;**29**:23-31.

FDA 2004

FDA. PCE® (erythromycin particles in tablets). Available at: http://www.fda.gov/medwatch/SAFETY/2004/mar_PI/PCE_PI.pdf (accessed July 2004).

Fung 1991

Fung CP, Powell M, Seymour A, Yuan M, Williams JD. The antimicrobial susceptibility of Moraxella catarrhalis isolated in England and Scotland in 1991. *Journal of Antimicrobial Chemotherapy* 1992;**30**:47-55.

Gonzales 2001a

Gonzales R, Bartlett JG, Besser RE, Hickner JM, Hoffman JR, Sande MA, et al. Principles of appropriate antibiotic use for treatment of nonspecific upper respiratory tract infections in adults: background. *Annals of Emergency Medicine* 2001;**37**(6):698-702.

Gonzales 2001b

Gonzales R, Malone DC, Maselli JH, Sande MA. Excessive antibiotic use for acute respiratory infections in the United States. *Clinical Infectious Disease* 2001;**33**(6):757-62.

Greiner 2003

Greiner O, Day PJ, Altwegg M, Nadal D. Quantitative detection of Moraxella catarrhalis in nasopharyngeal secretions by real-time PCR. *Journal of Clinical Microbiology* 2003;**41**(4):1386-90.

Guyatt 2013

Guyatt GH, Oxman AD, Santesso N, Helfand M, Vist G, Kunz R, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *Journal of Clinical Epidemiology* 2013;**66**(2):158-72.

Hashiguchi 1992

Hashiguchi K, Ogawa H, Kazuyama Y. Seroprevalence of Chlamydia pneumoniae infections in otolaryngeal diseases. *Journal of Laryngology and Otology* 1992;**106**:208.

Higgins 1974

Higgins PB. Viruses associated with acute respiratory infections 1961-71. *Journal of Hygiene* 1974;**72**(3):425-32.

Higgins 2011

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org. Chichester, UK: Wiley-Blackwell, 2011.

Hol 1996

Hol C, Schalen C, Verduin CM, Van Dijke EE, Verhoef J, Fleer A. Moraxella catarrhalis in acute laryngitis: infection or colonization?. *Journal of Infectious Diseases* 1996;**174**(3):636-8.

Jacobs 2004

Jacobs MR, Bajaksouzian S, Windau A, Good CE, Lin G, Pankuch GA, et al. Susceptibility of Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis to 17 oral antimicrobial agents based on pharmacodynamic parameters: 1998-2001 US Surveillance Study. *Clinics in Laboratory Medicine* 2004;**24**:503-30.

Jorgensen 1990

Jorgensen JH, Doern GV, Maher LA, Howell AW, Redding JS. Antimicrobial resistance among respiratory isolates of Haemophilus influenzae, Moraxella catarrhalis, and Streptococcus pneumoniae in the United States. *Antimicrobial Agents and Chemotherapy* 1990;**34**(11):2075-80.

Koufman 1996

Koufman JA. Infectious and inflammatory diseases of the larynx. In: Ballenger JJ, Snow JB editor(s). Otorhinolaryngology. Fifteenth. Philadelphia: Williams and Wilkins (Lea & Febiger), 1996:535-55.

Lefevbre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Lemiengre 2012

Lemiengre MB, van Driel ML, Merenstein D, Young J, De Sutter AI. Antibiotics for clinically diagnosed acute rhinosinusitis in adults. *Cochrane Database of Systematic Reviews* 2012, Issue 10. [DOI: 10.1002/14651858.CD006089.pub4]

Lund 2004

Lund VJ, Grouin JM, Eccles R, Bouter C, Chabolle F. Efficacy of fusafungine in acute rhinopharyngitis: a pooled analysis. *Rhinology* 2004;**42**(4):207-12.

Malmvall 2007

Malmvall BE, Molstad S, Darelid J, Hiselius A, Larsson L, Swanberg J, et al. Reduction of antibiotics sales and sustained low incidence of bacterial resistance: report on a broad approach during 10 years to implement evidence-based indications for antibiotic prescribing in Jonkoping County, Sweden. *Quality Management in Health Care* 2007;**16**(1):60-7.

Mazzaglia 1998

Mazzaglia G, Greco S, Lando C, Cucinotta G, Caputi AP, Mazzaglia G. Adult acute upper respiratory tract infections in Sicily: pattern of antibiotic drug prescription in primary care. *Journal of Antimicrobial Chemotherapy* 1998;**41**(2):259-66.

McAuley 2000

McAuley L, Pham B, Tugwell P, Moher D. Does the inclusion of grey literature influence estimates of intervention effectiveness reported in meta-analyses?. *Lancet* 2000;**356**:1228-31.

McAvoy 1994

McAvoy B, Davis P, Raymont A, Gribben B. The Waikato Medical Care Survey. *New Zealand Medical Journal* 1994;**107**:387-433.

McCaig 1995

McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. *JAMA* 1995;**273**(3):214-9.

McGregor 1995

McGregor A, Dovey S, Tilyard M. Antibiotic use in upper respiratory tract infections in New Zealand. *Family Practice* 1995;**12**:166-70.

Periti 1993

Periti P, Mazzei T, Mini E, Novelli A. Adverse effects of macrolide antibacterials. *Drug Safety* 1993;**9**(5):346-64.

Post 1995

Post JC, Preston RA, Aul JJ, Larkins-Pettigrew M, Rydquist-White J, Anderson KW, et al. Molecular analysis of bacterial pathogens in otitis media with effusion. *JAMA* 1995;**273**:1598-604.

Post 1996

Post JC, White J, Aul JJ, Zavoral T, Wadowsky RM, Zhang Y, et al. Development and validation of a multiplex PCR-based assay for the upper respiratory tract bacterial pathogens Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis. *Molecular Diagnosis* 1996;**1**:29-39.

Postma 1998

Postma GN, Koufman JA. Laryngitis. In: Bailey BJ editor(s). Head and Neck Surgery - Otolaryngology. Second Edition. Philadelphia: Lippincott-Raven, 1998:731-9.

RevMan 2014 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Schalen 1980

Schalen L, Christensen P, Kamme C, Miorner H, Pettersson KI, Schalen C. High isolation rate of Branhamella catarrhalis from the nasopharynx in adults with acute laryngitis. *Scandinavian Journal of Infectious Diseases* 1980;**12**(4):277-80.

Schalen 1988

Schalen L. Acute laryngitis in adults: diagnosis, etiology, treatment. *Acta Oto-Laryngologica* 1988;**449**:31.

Spiegel 2000

Spiegel JR, Hawkshaw M, Markiewicz A, Sataloff RT. Acute laryngitis. *Ear, Nose, and Throat Journal* 2000;**79**(7):488.

Spinks 2013

Spinks A, Glasziou PP, Del Mar C. Antibiotics for sore throat. *Cochrane Database of Systematic Reviews* 2013, Issue 11. [DOI: 10.1002/14651858.CD000023.pub4]

Steinman 2003a

Steinman MA, Landefeld CS, Gonzales R. Predictors of broad-spectrum antibiotic prescribing for acute respiratory tract infections in adult primary care. *JAMA* 2003;**289**(6):719-25.

Steinman 2003b

Steinman MA, Gonzales R, Linder JA, Landefeld CS. Changing use of antibiotics in community-based outpatient practice, 1991-1999. *Annals of Internal Medicine* 2003;**138**(7):525-33.

Steinman 2009

Steinman MA, Yang KY, Byron SC, Maselli JH, Gonzales R. Variation in outpatient antibiotic prescribing in the United States. *American Journal of Managed Care* 2009;**15**(12):861-8.

Sun 2006

Sun C, Jew S, Dasta SL. Osteopathic physicians in the United States: antibiotic prescribing practices for patients with nonspecific upper respiratory tract infections. *Journal of the American Osteopathic Association* 2006;**106**(8):450-5.

Vaughan 1982

Vaughan CW. Current concepts in otolaryngology: diagnosis and treatment of organic voice disorders. *New England Journal of Medicine* 1982;**307**(14):863-6.

Verduin 2002

Verduin CM, Hol C, Fleer A, van Dijk H, van Belkum A. Moraxella catarrhalis: from emerging to established pathogen. *Clinical Microbiology Reviews* 2002;**15**(1):125-44.

Wallace 1990

Wallace RJ, Nash DR, Steingrube VA. Antibiotic susceptibilities and drug resistance in Moraxella (Branhamella) catarrhalis. *American Journal of Medicine* 1990;**88**:46S-50S.

Wang 2003

Wang H, Yu YS, Liu Y, Li HY, Hu BJ, Sun ZY, et al. Resistance surveillance of common community respiratory pathogens isolated in China, 2002-2003 (abstract). *Zhonghua Jie He He Hu Xi Za Zhi* 2004;**27**(3):155-60.

WHO 2003

WHO. Upper respiratory tract infections. http://apps.who.int/medicinedocs/en/d/Js5406e/3.html (accessed 24 September 2003) 2003.

WHO 2014

World Health Organization. Antimicrobial resistance: global report on surveillance. Available at http://apps.who.int/iris/bitstream/10665/112642/1/9789241564748_eng.pdf (accessed 3 February 2015) 2014.

Wirtz 2010

Wirtz VJ, Dreser A, Gonzales R. Trends in antibiotic utilization in eight Latin American countries, 1997-2007. *Revista Panamericana de Salud Pública* 2010;**27**(3):219-25.

References to other published versions of this review

Ospina 2004

Ospina EG, Reveiz L, Cardona AF, Granados CE, Osorio JV. Antibiotics for acute laryngitis in adults. *Cochrane Database of Systematic Reviews* 2004, Issue 2. [DOI: 10.1002/14651858.CD004783]

Reveiz 2005

Reveiz L, Cardona AF, Ospina EG. Antibiotics for acute laryngitis in adults. *Cochrane Database of Systematic Reviews* 2005, Issue 1. [DOI: 10.1002/14651858.CD004783.pub2]

Reveiz 2007

Reveiz L, Cardona AF, Ospina EG. Antibiotics for acute laryngitis in adults. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD004783.pub3]

Reveiz 2009

Reveiz L, Cardona AF, Ospina EG. Antibiotics for acute laryngitis in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD004783.pub3]

Reveiz 2011

Reveiz L, Cardona AF, Ospina EG. Antibiotics for acute laryngitis in adults. *Cochrane Database of Systematic Reviews* 2011, Issue 5. [DOI: 10.1002/14651858.CD004783.pub3]

Reveiz 2013

Reveiz L, Cardona AF. Antibiotics for acute laryngitis in adults. *Cochrane Database of Systematic Reviews* 2013, Issue 3. [DOI: 10.1002/14651858.CD004783.pub4]

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Rafalskiy 2012

Methods	Prospective, randomised, comparative study
Participants	145* patients ≥ 18 years with symptoms of acute laryngitis were included in the study
Interventions	Patients ≥ 18 years with symptoms of acute laryngitis. Patients were randomly divided into 3 groups: Group 1: 7-day course of fusafungine (Bioparox®, Servier) (6 times a day by inhalations), Group 2: 7-day course of fusafungine (Bioparox®, Servier) (6 times a day by inhalations) plus clarithromycin (Clacid®, Abbott) (250 mg bid 7 days) and Group 3: no treatment
Outcomes	Clinical cure rates; adverse events. The results of the clinical investigations were collected on days 5 ± 1 (V2), 8 ± 1 (V3) and 28 ± 2 (V4) after the first dose of medication
Notes	Reported as an abstract in the 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) 9 to 12 September 2012. A full report was not available *While the authors reported in the abstract that 125 patients were randomised, the total number of participants in the 3 groups totalled 145 No information on funding sources was provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) All outcomes	High risk	Not reported, probably not performed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported, probably not performed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	At visit 3 (day 8 ± 1) no losses were reported, at visit 4 (day 28 ± 1) 72% were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Not reported
Other bias	High risk	Baseline characteristics were not reported. Case definition of laryngitis was not defined

Schalén 1985

Methods	Randomised, double-blind, controlled trial
Participants	Adult patients aged over 18 with a history of acute laryngitis defined as hoarseness associated with other symptoms of upper respiratory tract infection Exclusion = patients with chronic relevant underlying diseases, symptoms of laryngitis for more than 3 weeks (chronic laryngitis) and antibiotic therapy within the preceding 2 weeks before diagnosis N = 100 Penicillin V: n = 51 Placebo: n = 49 No drop-outs
Interventions	Penicillin V 0.8 g bid for 5 days Placebo
Outcomes	Objective voice scores. No statistical difference was found between the 2 groups Symptoms judged by the patients. No differences were found between the 2 groups Bacteriological findings. The isolation rates of pathogens at the acute and follow-up visits after 1 and 2 weeks did not differ significantly between the 2 groups
Notes	No information on funding sources was provided

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Double blind study". No mention of randomisation
Allocation concealment (selection bias)	Unclear risk	No details mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	"Double blind". "Identical placebo". It was not clear who was blinded
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Low risk	No drop-outs
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Low risk	Baseline characteristics mentioned

Schalén 1993

Methods	Randomised, double-blind, controlled trial
Participants	Adult patients aged over 18 with a history of acute laryngitis defined as hoarseness associated with other symptoms of upper respiratory tract infection accompanied by inflammatory signs in the laryngeal, pharyngeal and nasal mucosa (increased vascular injection, purulent secretion, oedema or any combination of these signs). Exclusion = patients with chronic relevant underlying diseases, symptoms of laryngitis for more than 3 weeks, history of allergy or intolerance to erythromycin, pregnancy and antibiotic therapy within the preceding 2 weeks before diagnosis N = 106 Erythromycin: n = 53 Placebo: n = 53 7 drop-outs
Interventions	Erythromycin 500 mg bid for 5 days Placebo
Outcomes	Objective voice scores. No statistical difference was found between the 2 groups Symptoms judged by the patients. At 1 week there were significant differences in the severity of reported vocal symptoms as judged by the patients, comparing the erythromycin and placebo groups (P value = 0.042). At 2 weeks significantly fewer complaints of cough were reported by the erythromycin group Bacteriological findings. There was no difference between the 2 groups in the recovery rate of pathogens at 2 weeks
Notes	No information on funding sources was provided

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised"
Allocation concealment (selection bias)	Unclear risk	No details mentioned
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double blind". "Identical tablets". It was not clear if outcome assessors were blinded
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit judgement of 'low risk' or 'high risk'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	15% lost to follow-up. No reasons mentioned
Selective reporting (reporting bias)	Unclear risk	The study protocol is not available
Other bias	Unclear risk	Baseline characteristics mentioned. The erythromycin group had a higher and more significant number of bacterial pathogens and *M. catarrhalis* was isolat-

Schalén 1993 *(Continued)*

	ed from the nasopharynx in this group (P value = 0.045 and P value = 0.012, Fisher's exact test)

N: number
bid: twice a day

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Schalén 1992	A preliminary report of the erythromycin trial (Schalén 1993)

DATA AND ANALYSES

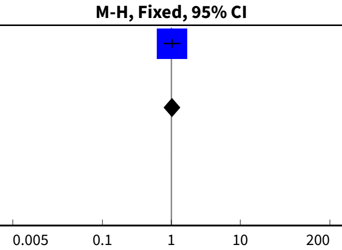
Comparison 1. Fusafungine versus fusafungine + clarithromycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure rates at day 5 ± 1	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.77, 1.35]
2 Clinical cure rates at day 8 ± 1	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.17]
3 Clinical cure rates at day 28 ± 2	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.80, 1.34]
4 Frequency of adverse events	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.19, 3.45]

Analysis 1.1. Comparison 1 Fusafungine versus fusafungine + clarithromycin, Outcome 1 Clinical cure rates at day 5 ± 1.

Study or subgroup	Fusafungine n/N	Fusafungine+clarithromycin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rafalskiy 2012	32/48	34/52		100%	1.02[0.77,1.35]
Total (95% CI)	**48**	**52**		**100%**	**1.02[0.77,1.35]**

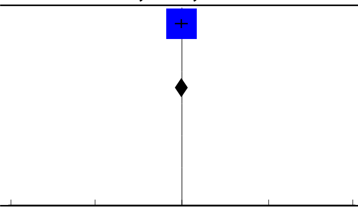
Total events: 32 (Fusafungine), 34 (Fusafungine+clarithromycin)
Heterogeneity: Not applicable
Test for overall effect: Z=0.14(P=0.89)



Favours fusafungine+clarithromycin | Favours fusafungine

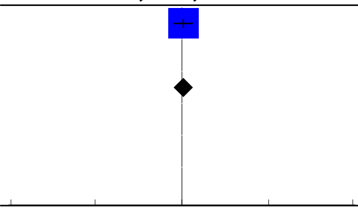
Analysis 1.2. Comparison 1 Fusafungine versus fusafungine + clarithromycin, Outcome 2 Clinical cure rates at day 8 ± 1.

Study or subgroup	Fusafungine	Fusafungine+clarithromycin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Rafalskiy 2012	40/48	44/52		100%	0.98[0.83,1.17]
Total (95% CI)	**48**	**52**		**100%**	**0.98[0.83,1.17]**
Total events: 40 (Fusafungine), 44 (Fusafungine+clarithromycin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.17(P=0.86)					
		Fusafungine+clarithromycin	0.01 0.1 1 10 100	Favours fusafungine	



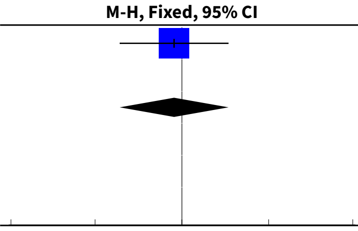
Analysis 1.3. Comparison 1 Fusafungine versus fusafungine + clarithromycin, Outcome 3 Clinical cure rates at day 28 ± 2.

Study or subgroup	Fusafungine	Fusafungine+clarithromycin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Rafalskiy 2012	18/21	19/23		100%	1.04[0.8,1.34]
Total (95% CI)	**21**	**23**		**100%**	**1.04[0.8,1.34]**
Total events: 18 (Fusafungine), 19 (Fusafungine+clarithromycin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.28(P=0.78)					
		Favours fusafungine+clarithromycin	0.01 0.1 1 10 100	Favours fusafungine	



Analysis 1.4. Comparison 1 Fusafungine versus fusafungine + clarithromycin, Outcome 4 Frequency of adverse events.

Study or subgroup	Fusafungine	Fusafungine+clarithromycin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Rafalskiy 2012	3/48	4/52		100%	0.81[0.19,3.45]
Total (95% CI)	**48**	**52**		**100%**	**0.81[0.19,3.45]**
Total events: 3 (Fusafungine), 4 (Fusafungine+clarithromycin)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=0.28(P=0.78)					
		Favours fusafungine	0.01 0.1 1 10 100	Favours fusafungine+clarithromycin	



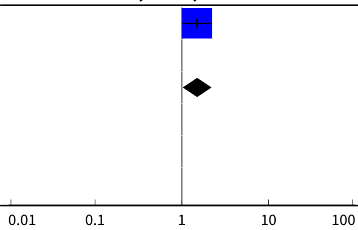
Comparison 2. Fusafungine versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure rates at day 5 ± 1	1	93	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [1.02, 2.20]
2 Clinical cure rates at day 8 ± 1	1	93	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.88, 1.31]
3 Clinical cure rates at day 28 ± 2	1	38	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.82, 1.54]

Analysis 2.1. Comparison 2 Fusafungine versus no treatment, Outcome 1 Clinical cure rates at day 5 ± 1.

Study or subgroup	Fusafungine n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rafalskiy 2012	32/48	20/45		100%	1.5[1.02,2.2]
Total (95% CI)	**48**	**45**		**100%**	**1.5[1.02,2.2]**

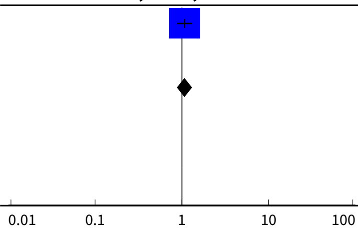
Total events: 32 (Fusafungine), 20 (No treatment)
Heterogeneity: Not applicable
Test for overall effect: Z=2.07(P=0.04)



Analysis 2.2. Comparison 2 Fusafungine versus no treatment, Outcome 2 Clinical cure rates at day 8 ± 1.

Study or subgroup	Funsafugine n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rafalskiy 2012	40/48	35/45		100%	1.07[0.88,1.31]
Total (95% CI)	**48**	**45**		**100%**	**1.07[0.88,1.31]**

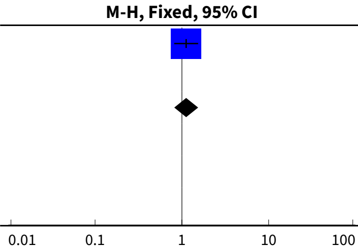
Total events: 40 (Funsafugine), 35 (No treatment)
Heterogeneity: Not applicable
Test for overall effect: Z=0.67(P=0.5)



Analysis 2.3. Comparison 2 Fusafungine versus no treatment, Outcome 3 Clinical cure rates at day 28 ± 2.

Study or subgroup	Fusafungine n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rafalskiy 2012	18/21	13/17		100%	1.12[0.82,1.54]
Total (95% CI)	**21**	**17**		**100%**	**1.12[0.82,1.54]**

Total events: 18 (Fusafungine), 13 (No treatment)
Heterogeneity: Not applicable
Test for overall effect: Z=0.71(P=0.48)

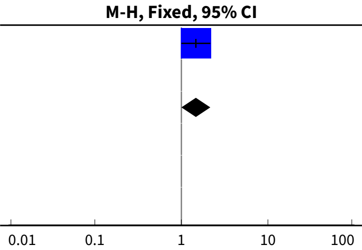


Comparison 3. Fusafungine + clarithromycin versus no treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical cure rates at day 5 ± 1	1	97	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.00, 2.16]
2 Clinical cure rates at day 8 ± 1	1	97	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.90, 1.32]
3 Clinical cure rates at day 28 ± 2	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.78, 1.49]

Analysis 3.1. Comparison 3 Fusafungine + clarithromycin versus no treatment, Outcome 1 Clinical cure rates at day 5 ± 1.

Study or subgroup	Fusafungine+clarithromycin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rafalskiy 2012	34/52	20/45		100%	1.47[1,2.16]
Total (95% CI)	**52**	**45**		**100%**	**1.47[1,2.16]**

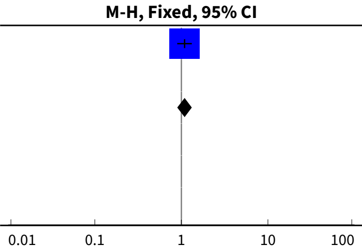


Total events: 34 (Fusafungine+clarithromycin), 20 (No treatment)
Heterogeneity: Not applicable
Test for overall effect: Z=1.98(P=0.05)

Favours no treatment | Favours fusafungine+clarithromycin

Analysis 3.2. Comparison 3 Fusafungine + clarithromycin versus no treatment, Outcome 2 Clinical cure rates at day 8 ± 1.

Study or subgroup	Fusafungine+clarithromycin n/N	No treatment n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rafalskiy 2012	44/52	35/45		100%	1.09[0.9,1.32]
Total (95% CI)	**52**	**45**		**100%**	**1.09[0.9,1.32]**

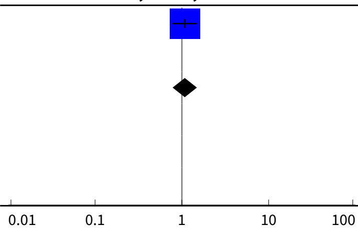


Total events: 44 (Fusafungine+clarithromycin), 35 (No treatment)
Heterogeneity: Not applicable
Test for overall effect: Z=0.85(P=0.4)

Favours no treatment | Favours fusafungine+clarithromycin

Analysis 3.3. Comparison 3 Fusafungine + clarithromycin versus no treatment, Outcome 3 Clinical cure rates at day 28 ± 2.

Study or subgroup	Fusa-fungine+clar-ithromycin	No treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Rafalskiy 2012	19/23	13/17		100%	1.08[0.78,1.49]
Total (95% CI)	**23**	**17**		**100%**	**1.08[0.78,1.49]**
Total events: 19 (Fusafungine+clarithromycin), 13 (No treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.47(P=0.64)					



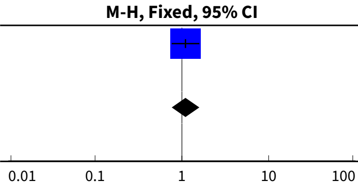
Favours no treatment | Favours fusafungine+clarithromycin

Comparison 4. Erythromycin versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Laryngitis at 1 week	1	99	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.76, 1.59]
2 Laryngitis at 2 week	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.44, 1.49]
3 Elimination rate of Moraxella ca-tarrhalis at 1 week	1	49	Risk Ratio (M-H, Fixed, 95% CI)	2.64 [1.34, 5.21]
4 Elimination rate of Moraxella ca-tarrhalis at 2 week	1	49	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.36, 1.82]
5 Patients having voice disturbance at week 1	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.90]
6 Patients having voice disturbance at week 2	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.28, 1.14]
7 Cough at week 1 (subjective symp-tom)	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.49, 1.11]
8 Cough at week 2 (subjective symp-tom)	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.15, 0.97]

Analysis 4.1. Comparison 4 Erythromycin versus placebo, Outcome 1 Laryngitis at 1 week.

Study or subgroup	Erythromycin	Placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Schalén 1993	27/48	26/51		100%	1.1[0.76,1.59]
Total (95% CI)	**48**	**51**		**100%**	**1.1[0.76,1.59]**
Total events: 27 (Erythromycin), 26 (Placebo)					



Favours erythromycin | Favours placebo

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=0.53(P=0.6)					
		Favours erythromycin	0.01 0.1 1 10 100	Favours placebo	

Analysis 4.2. Comparison 4 Erythromycin versus placebo, Outcome 2 Laryngitis at 2 week.

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schalén 1993	13/48	17/51		100%	0.81[0.44,1.49]
Total (95% CI)	**48**	**51**		**100%**	**0.81[0.44,1.49]**
Total events: 13 (Erythromycin), 17 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.67(P=0.5)					
		Favours erythromycin	0.01 0.1 1 10 100	Favours placebo	

Analysis 4.3. Comparison 4 Erythromycin versus placebo, Outcome 3 Elimination rate of Moraxella catarrhalis at 1 week.

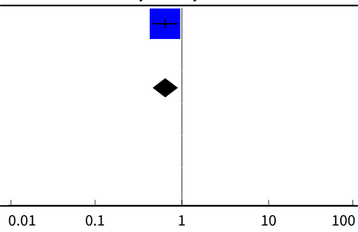
Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schalén 1993	25/30	6/19		100%	2.64[1.34,5.21]
Total (95% CI)	**30**	**19**		**100%**	**2.64[1.34,5.21]**
Total events: 25 (Erythromycin), 6 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.79(P=0.01)					
		Favours placebo	0.01 0.1 1 10 100	Favours erythromycin	

Analysis 4.4. Comparison 4 Erythromycin versus placebo, Outcome 4 Elimination rate of Moraxella catarrhalis at 2 week.

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schalén 1993	9/30	7/19		100%	0.81[0.36,1.82]
Total (95% CI)	**30**	**19**		**100%**	**0.81[0.36,1.82]**
Total events: 9 (Erythromycin), 7 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.5(P=0.62)					
		Favours erythromycin	0.01 0.1 1 10 100	Favours placebo	

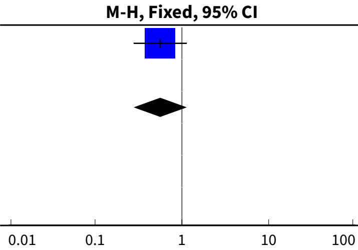
Analysis 4.5. Comparison 4 Erythromycin versus placebo, Outcome 5 Patients having voice disturbance at week 1.

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schalén 1993	23/48	38/51		100%	0.64[0.46,0.9]
Total (95% CI)	**48**	**51**		**100%**	**0.64[0.46,0.9]**
Total events: 23 (Erythromycin), 38 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.58(P=0.01)					



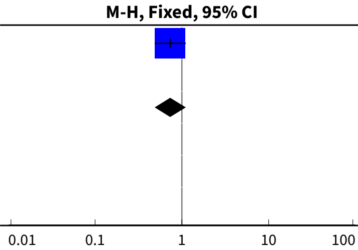
Analysis 4.6. Comparison 4 Erythromycin versus placebo, Outcome 6 Patients having voice disturbance at week 2.

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schalén 1993	9/48	17/51		100%	0.56[0.28,1.14]
Total (95% CI)	**48**	**51**		**100%**	**0.56[0.28,1.14]**
Total events: 9 (Erythromycin), 17 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.6(P=0.11)					



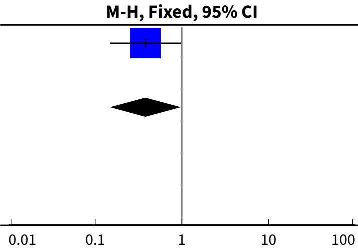
Analysis 4.7. Comparison 4 Erythromycin versus placebo, Outcome 7 Cough at week 1 (subjective symptom).

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schalén 1993	20/48	29/51		100%	0.73[0.49,1.11]
Total (95% CI)	**48**	**51**		**100%**	**0.73[0.49,1.11]**
Total events: 20 (Erythromycin), 29 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.48(P=0.14)					



Analysis 4.8. Comparison 4 Erythromycin versus placebo, Outcome 8 Cough at week 2 (subjective symptom).

Study or subgroup	Erythromycin n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Schalén 1993	5/48	14/51		100%	0.38[0.15,0.97]
Total (95% CI)	**48**	**51**		**100%**	**0.38[0.15,0.97]**
Total events: 5 (Erythromycin), 14 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.02(P=0.04)					



APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE (OVID)

1 exp Laryngitis/
2 laryngit*.tw.
3 Laryngeal diseases/
4 Laryngeal Edema/
5 laryngeal*.tw.
6 Epiglottitis/
7 epiglottit*.tw.
8 pharyngolaryngit*.tw.
9 laryngotracheit*.tw.
10 Hoarseness/
11 hoarse*.tw.
12 supraglottit*.tw.
13 Voice Disorders/
14 Voice Quality/
15 (voice adj2 (disturb* or los* or quality or disorder* or croak*)).tw.
16 or/1-15
17 exp Larynx/
18 larynx.tw.
19 exp Laryngeal Mucosa/
20 laryng*.tw.
21 Epiglottis/
22 epiglott*.tw.
23 exp Glottis/
24 glottis.tw.
25 Hypopharynx/
26 laryngopharyn*.tw.
27 hypopharyn*.tw.
28 Vocal Cords/
29 vocal cord*.tw.
30 supraglott*.tw.
31 nasopharynx.tw.
32 subglottic.tw.
33 or/17-32
34 (irritat* or sore* or infect* or inflam* or redness).tw.
35 33 and 34
36 16 or 35
37 exp Anti-Bacterial Agents/
38 antibiotic*.tw.
39 (azithromycin* or clarithromycin* or erythromycin* or roxithromycin* or macrolide*).tw.
40 (cefamandole* or cefoperazone* or cefazolin* or cefonicid* or cefsulodin* or cephacetrile* or cefotaxime* or cephalothin* or cephapirin* or cephalexin* or cephaclor* or cephadroxil* or cephaloglycin* or cephradine* or cephaloridine* or ceftazidime* or cephamycin* or cefmetazole* or cefotetan* or cefoxitin* or cephalosporin*).tw.
41 (amoxicillin* or ampicillin* or sulbactum* or tetracyclin* or clindamycin* or lincomycin* or doxycyclin*).tw.
42 (fluoroquinolone* or ciprofloxacin* or fleroxacin* or enoxacin* or norfloxacin* or ofloxacin* or pefloxacin* or moxifloxacin* or esparfloxacin* or clindamicin*).tw.
43 (penicillin* or ticarcillin* or lactam* or levofloxacin* or trimethoprim*).tw.
44 or/37-43
45 36 and 44

Appendix 2. EMBASE search strategy

#37. #33 AND #36
#36. #34 OR #35

#35. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti
#34. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#33. #24 AND #32
#32. #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
#31. penicillin*:ab,ti OR ticarcillin*:ab,ti OR lactam*:ab,ti OR levofloxacin*:ab,ti OR trimethoprim*:ab,ti
#30. fluoroquinolone*:ab,ti OR ciprofloxacin*:ab,ti OR fleroxacin*:ab,ti OR enoxacin*:ab,ti OR norfloxacin*:ab,ti OR ofloxacin*:ab,ti OR pefloxacin*:ab,ti OR moxifloxacin*:ab,ti OR esparfloxacin*:ab,ti OR clindamicin*:ab,ti OR clindamycin*:ab,ti
#29. amoxicillin*:ab,ti OR amoxycillin*:ab,ti OR ampicillin*:ab,ti OR sulbactum*:ab,ti OR tetracyclin*:ab,ti OR clindamycin*:ab,ti OR lincomycin*:ab,ti OR doxycyclin*:ab,ti
#28. cefamandole*:ab,ti OR cefoperazone*:ab,ti OR cefazolin*:ab,ti OR cefonicid*:ab,ti AND cefsulodin*:ab,ti OR cephacetrile*:ab,ti OR cefotaxime*:ab,ti OR cephalothin*:ab,ti OR cephapirin*:ab,ti OR cephalexin*:ab,ti OR cephaclor*:ab,ti OR cephadroxil*:ab,ti OR cephaloglycin*:ab,ti OR cephradine*:ab,ti OR cephaloridine*:ab,ti OR ceftazidime*:ab,ti OR cephamycin*:ab,ti OR cefmetaxole*:ab,ti OR cefotetan*:ab,ti OR cefoxitin*:ab,ti OR cephalosporin*:ab,ti
#27. azithromycin*:ab,ti OR clarithromycin*:ab,ti OR erythromycin*:ab,ti OR roxithromycin*:ab,ti OR macrolide*:ab,ti
#26. antibiotic*:ab,ti
#25. 'antibiotic agent'/exp
#24. #12 OR #23
#23. #19 AND #22
#22. #20 OR #21
#21. hoarse*:ab,ti OR irritat*:ab,ti OR sore*:ab,ti OR croak*:ab,ti OR infect*:ab,ti OR inflamm*:ab,ti OR redness:ab,ti
#20. (voice NEAR/3 (loss OR lost OR disturb*)):ab,ti
#19. #13 OR #14 OR #15 OR #16 OR #17 OR #18
#18. nasopharynx:ab,ti OR subglottic:ab,ti OR supraglott*:ab,ti
#17. 'nasopharynx'/de
#16. hypopharynx:ab,ti OR laryngopharynx:ab,ti
#15. 'hypopharynx'/de
#14. larynx:ab,ti OR laryng*:ab,ti OR epiglott*:ab,ti OR glottis:ab,ti OR 'vocal cord':ab,ti OR 'vocal cords':ab,ti
#13. 'larynx'/de OR 'epiglottis'/de OR 'glottis'/exp OR 'larynx mucosa'/de OR 'vocal cord'/exp
#12. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
#11. supraglottit*:ab,ti
#10. hoarse*:ab,ti
#9. 'hoarseness'/de
#8. pharyngolaryngit*:ab,ti OR laryngotracheit*:ab,ti
#7. epiglottit*:ab,ti
#6. 'epiglottitis'/exp
#5. laryngeal*:ab,ti
#4. 'larynx edema'/de
#3. 'larynx disorder'/de
#2. laryngit*:ab,ti
#1. 'laryngitis'/exp

Appendix 3. LILACS search strategy

((mh:laryngitis OR laryngit* OR laringit* OR mh:c08.360.535* OR mh:c08.730.368* OR mh:c09.400.535* OR mh:"Laryngeal Diseases" OR "Enfermedades de la Laringe" OR "Doenças da Laringe" OR laringopatias OR mh:"Laryngeal Edema" OR "Edema Laríngeo" OR laryngeal* OR mh:epiglottitis OR epiglottit* OR epiglotitis OR epiglotite OR pharyngolaryngit* OR laryngotracheit* OR mh:hoarseness OR ronquera OR rouquidão OR hoars* OR supraglottit* OR mh:"Voice Disorders" OR "Trastornos de la Voz" OR "Distúrbios da Voz" OR mh:"Voice Quality" OR "Calidad de la Voz" OR "Qualidade da Voz" OR "voice disturbance") OR ((voice OR voz) AND (disturb* OR los* OR quality OR disorder* OR croak*)) OR ((mh:larynx OR mh:a04.329* OR laringe OR larynx OR mh:"Laryngeal Mucosa" OR "Mucosa Laríngea" OR laryng* OR mh:epiglottis OR epiglotis OR epiglote OR epiglot* OR mh:glottis OR glotis OR glote OR mh:a04.329.364* OR glot* OR mh:hypopharynx OR hipofaringe OR hipofaringe OR hypopharynx OR laryngopharynx OR laringofaringe OR "vocal cords" OR "Pliegues Vocales" OR "Pregas Vocais" OR supraglot* OR nasopharynx OR subglottic) AND (infect* OR infecciones* OR infecções OR inflam* OR inflamación OR inflamação OR redness OR irritat*))) AND (mh:"Anti-Bacterial Agents" OR mh:d27.505.954.122.085* OR antibacterianos OR antibiotic* OR antibióticos OR mh:d02.540.505.250* OR mh:erythromycin OR eritromicina OR erythromycin OR mh:azithromycin OR azitromicina OR azithromycin OR clarithromycin OR claritromicina OR mh:roxithromycin OR roxithromycin OR roxitromicina OR mh:macrolides OR macrolide* OR macrólidos OR macrolídeos OR mh:cephalosporins OR cephalosporin* OR mh:d02.065.589.099.249* OR mh:d02.886.665.074* OR mh:d04.075.080.875.099.221.249* OR cefalosporin* OR cefamandole* OR cefoperazone* OR cefazolin* OR cefonicid* OR cefsulodin* OR cephacetrile* OR cefotaxime* OR cephalothin* OR cephapirin* OR cephalexin* OR cephaclor* OR cephadroxil* OR cephaloglycin* OR cephradine* OR cephaloridine* OR ceftazidime* OR cephamycin* OR cefmetazole* OR cefotetan* OR cefoxitin* OR mh:penicillins OR penicilinas OR mh:d02.065.589.099.750* OR mh:d02.886.108.750* OR mh:d03.438.260.825* OR mh:d03.605.084.737* OR mh:d04.075.080.875.099.221.750* OR penicillin* OR amoxicil* OR ampicil* OR sulbactam OR mh:tetracyclines OR tetracyclin* OR tetraciclina OR mh:clindamycin OR clindamycin OR clindamicina OR mh:lincomycin OR lincomycin OR lincomicina OR mh:doxycycline OR doxycyclin* OR doxiciclina OR mh:fluoroquinolones OR mh:d03.438.810.835.322* OR fluoroquinolon* OR ciprofloxacin* OR fleroxacin* OR enoxacin* OR norfloxacin* OR ofloxacin* OR pefloxacin* OR moxifloxacin* OR esparfloxacin* OR clindamicin* OR ticarcillin OR ticarcilina OR lactam* OR levofloxacin* OR trimethoprim* OR trimetoprim* OR mh:trimethoprim OR mh:d03.383.742.906*) AND db:("LILACS") AND type_of_study:("clinical_trials")

Appendix 4. Biosis Previews search strategy

# 4	5	#2 AND #1 Refined by: Publication Years=(2011 OR 2012) *Databases=BIOSIS Previews Timespan=All Years*
# 3	74	#2 AND #1 *Databases=BIOSIS Previews Timespan=All Years*
# 2	662,165	Topic=(random* or placebo* or crossover* or "cross over" or allocat* or ((singl* or doubl*) NEAR/1 blind*)) OR Title=(trial) *Databases=BIOSIS Previews Timespan=All Years*
# 1	1,339	Topic=(laryng* or larynx* or epiglott* or glottis or laryngopharyng* or hypopharynx or "vocal cord*" or hoarse* or supraglott* or pharyngolaryng* or nasopharynx or subglottic or laryngotracheit*) AND Topic=(antibiotic* or azithromycin* or clarithromycin* or erythromycin* or roxithromycin* or macrolide* or efamandole* or cefoperazone* or cefazolin* or cefonicid* or cefsulodin* or cephacetrile* or cefotaxime* or cephalothin* or cephapirin* or cephalexin* or cephaclor* or cephadroxil* or cephaloglycin* or cephradine* or cephaloridine* or ceftazidime* or cephamycin* or cefmetazole* or cefotetan* or cefoxitin* or cephalosporin* or amoxicillin* or ampicillin* or sulbactum* or tetracyclin* or clindamycin* or lincomycin* or doxycyclin* or fluoroquinolone* or ciprofloxacin* or fleroxacin* or enoxacin* or norfloxacin* or ofloxacin* or pefloxacin* or moxifloxacin* or esparfloxacin* or clindamicin* or penicillin* or ticarcillin* or lactam* or levofloxacin* or trimethoprim*) *Databases=BIOSIS Previews Timespan=All Years*

Appendix 5. Previous search strategies

For the last update (January 2013) we searched the Cochrane Central Register of Controlled Trials (CENTRAL 2012, Issue 12), MEDLINE (January 2011 to January week 3, 2013), EMBASE (January 2011 to January 2013), LILACS (January 2011 to January 2013) and BIOSIS (January 2011 to January 2013).

For the 2011 update we searched the Cochrane Central Register of Controlled Trials (CENTRAL 2011, Issue 1), which includes the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (November 2008 to January week 3, 2011), EMBASE (November 2008 to February 2011), LILACS (November 2008 to February 2011) and BIOSIS (November 2008 to February 2011).

Prior to this we searched the Cochrane Central Register of Controlled Trials (CENTRAL 2008, Issue 4), which includes the Cochrane Acute Respiratory Infections (ARI) Group's Specialised Register, MEDLINE (January 1966 to November Week 2 2008), EMBASE (1974 to November 2008), LILACS (from 1982 to November 2008) (Castro 1997) and BIOSIS (1980 to November 2008).

MEDLINE was searched using the following updated list of keywords and MeSH terms in conjunction with the highly sensitive search strategy designed by the Cochrane Collaboration for identifying RCTs. The same strategy was used to search CENTRAL and adapted to search EMBASE, LILACS and BIOSIS. See below for the original MEDLINE search strategy.

MEDLINE (OVID)

1 exp Laryngitis/
2 laryngit*.tw.
3 Laryngeal Edema/
4 Epiglottitis/
5 epiglottit*.tw.
6 pharyngolaryngit*.tw.
7 laryngotracheit*.tw.
8 or/1-7
9 exp Larynx/
10 larynx.tw.
11 exp Laryngeal Mucosa/
12 laryng*.tw.
13 Epiglottis/
14 epiglott*.tw.
15 exp Glottis/
16 glottis.tw.
17 Hypopharynx/
18 hypopharynx.tw.
19 laryngopharyn*.tw.
20 hypopharyn*.tw.
21 Vocal Cords/
22 vocal cord*.tw.
23 supraglott*.tw.
24 nasopharynx.tw.
25 subglottic.tw.
26 or/9-25
27 exp Voice Disorders/
28 Voice Quality/
29 (voice adj2 disturbanc*).tw.
30 hoarse*.tw.
31 infection*.tw.
32 inflammation*.tw.
33 redness.tw.
34 (los* adj3 voice).tw.
35 or/27-33
36 35 and 26
37 8 or 36
38 exp Anti-Bacterial Agents/
39 antibiotic*.tw.
40 (azithromycin* or clarithromycin* or erythromycin* or roxithromycin* or macrolide*).tw.
41 (cefamandole* or cefoperazone* or cefazolin* or cefonicid* or cefsulodin* or cephacetrile* or cefotaxime* or cephalothin* or cephapirin* or cephalexin* or cephaclor* or cephadroxil* or cephaloglycin* or cephradine* or cephaloridine* or ceftazidime* or cephamycin* or cefmetazole* or cefotetan* or cefoxitin* or cephalosporin*).tw.
42 (amoxicilline* or ampicillin* or sulbactum* or tetracycline* or clindamycin* or lincomycin* or doxycycline*).tw.
43 (floroquinolone* or ciprofloxacin* or fleroxacin* or enoxacin* or norfloxacin* or ofloxacin* or pefloxacin* or moxifloxacin* or esparfloxacin* or clindamicin*).tw.
44 (penicillin* or ticarcillin* or lactam* or levofloxacin* or trimethoprim*).tw.
45 or/38-44
46 45 and 37
47 randomized controlled trial.pt.
48 controlled clinical trial.pt.
49 randomized.ab.
50 placebo.ab.
51 drug therapy.fs.
52 randomly.ab.
53 trial.ab.

54 groups.ab.
55 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54
56 (animals not (humans and animals)).sh.
57 55 not 56
58 57 and 46

Original MEDLINE search strategy

1 exp Laryngitis/
2 Larynx/
3 exp Laryngeal Diseases/
4 Laryngeal Edema/
5 Laryngeal Mucosa/
6 Epiglottitis/
7 Glottis/
8 Epiglottis/
9 Hypopharynx/
10 laryngopharyn*.tw.
11 Vocal Cords/
12 Hoarseness/
13 (laryngitis or larynx or laryngeal).tw.
14 (epiglottitis or epiglottis).tw.
15 (vocal adj3 cord*).tw.
16 hoarse*.tw.
17 supraglottitis.tw.
18 (pharyngolaryngitis or nasopharynx or subglottic).tw.
19 laryngotracheitis.tw.
20 or/1-19
21 exp Anti-Bacterial Agents/
22 antibiotic*.tw.
23 (azithromycin* or clarithromycin* or erythromycin* or roxithromycin* or macrolide*).tw.
24 (cefamandole* or cefoperazone* or cefazolin* or cefonicid* or cefsulodin* or cephacetrile* or cefotaxime* or cephalothin* or cephapirin* or cephalexin* or cephaclor* or cephadroxil* or cephaloglycin* or cephradine* or cephaloridine* or ceftazidime* or cephamycin* or cefmetazole* or cefotetan* or cefoxitin* or cephalosporin*).tw.
25 (amoxicilline* or ampicillin* or sulbactum* or tetracycline* or clindamycin* or lincomycin* or doxycycline*).tw.
26 (floroquinolone* or ciprofloxacin* or fleroxacin* or enoxacin* or norfloxacin* or ofloxacin* or pefloxacin* or moxifloxacin* or esparfloxacin* or clindamicin*).tw.
27 (penicillin* or ticarcillin* or lactam* or levofloxacin* or trimethoprim*).tw.
28 or/21-27
29 28 and 20
30 randomized controlled trial.pt.
31 controlled clinical trial.pt.
32 randomized.ab.
33 placebo.ab.
34 drug therapy.fs.
35 randomly.ab.
36 trial.ab.
37 groups.ab.
38 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39 (animals not (humans and animals)).sh.
40 38 not 39
41 40 and 29

FEEDBACK

Antibiotics for acute laryngitis in adults, 17 November 2012

Summary

This is a translated summary of feedback submitted in German

This review highlights the relative ineffectiveness of antibiotics in viral-induced laryngitis which is consistent with clinical experience.

Acute laryngitis requires more than a clinical diagnosis and in the absence of laryngoscopic findings, cannot be clearly diagnosed. The studies included in the review used clinical parameters for assessment. This is not an accurate diagnostic approach, since a more specialised examination of the organ is required.

Detailed examination by an ENT specialist is therefore essential for a more accurate diagnosis, in order to make a treatment decision.

In my opinion pure acute laryngitis is therefore an unusual diagnosis. In clinic, we classify it as rhino-pharyngolaryngitis or often rhinosinubronchitis with the larynx as its inevitable anatomical manifestation. The involvement of the larynx in a viral infection of the respiratory tract is clearly only part of a disease whose course is often biphasic and regularly leads to bacterial superinfection with extensions to the upper and lower respiratory tract. The corresponding culture confirms this and probably explains the better effect of erythromycin over penicillin V, which has a relatively narrow spectrum of activity. In clinical practice amoxicillin or azithromycin have become established macrolide antibiotics.

We do not know why many patients experience hoarseness primarily in the context of a common cold. Apparently there are individual areas of involvement of the respiratory system, which relate to the pathogen spectrum and to known pre-existing conditions such as allergies, asthma and chronic sinusitis. These are necessary for differential diagnosis.

Just as often, important differential diagnoses are excluded from an ENT medical examination of the vocal cord paresis (often as the primary symptom of bronchial carcinoma), incidental findings (such as vocal cord nodules), intubation granuloma or posterior laryngitis with reflux gastritis.

In contrast, in pure acute laryngitis the lupen laryngoscopic findings often appear inconspicuous, making them more characteristic of the findings and part of diagnosis. Most microscopically visible change is, depending on the stage of the disease, streaky redness and visible blood vessels in the vocal cords. Monochorditis associated with tuberculosis can also be determined.

ENT examination including nasal and laryngeal endoscopy enables more targeted treatment decisions, with the aim of avoiding unnecessary antibiotic therapy. This is not a frequent outcome, since prognostic assessment of the disease process includes age, immune status, smoking, co-morbidities such as OSA and COPD, and relative dryness of mouth especially with concomitant antihypertensives or pre-existing laryngeal diseases.

Due to the protracted nature of this condition, patients may expect additional antibiotic therapy. However, achieving effective treatment with systemic application is hampered by the poor blood supply to the vocal cords.

The most important therapy in acute laryngitis is total voice rest. This is difficult for people who undertake work which requires them to talk. Humidification of the respiratory tract by inhalation, supplemented with mucolytics, sage and thyme, can reduce inflammation of the larynx caused by the surrounding laryngeal mucosa and can alleviate symptoms. Consideration of concomitant risk factors should be flagged up as part of the investigation and taken into consideration along with other indications for treatment.

There is a lack of data showing the extent to which early treatment with antibiotic therapy can prevent pneumonia in the elderly.

Since reviews published in the Cochrane Library are gaining acceptance as part of evidence-based medicine which serves as a basis for further patient care, there should also be a general statement on the necessary differential diagnosis. Hoarseness as a symptom is not the sole criterion for the assessment of a disease. The task of good clinical practice may be to provide treatment protocols which take account of individual factors and which apply a more evidence-based approach to the treatment of disease. To this end, the Cochrane Library provides a good basis for discussion.

The original feedback comment

Der Artikel Antibiotics for acute laryngitis in adults unterstreicht die relative Wirkungslosigkeit von Antibiotika bei einer viral ausgelösten Laryngitis. Dies entspricht der klinischen Erfahrung.

Die akute Laryngitis ist mehr als eine klinische Diagnose. Ohne laryngoskopischen Befund kann diese Diagnose nicht eindeutig gestellt werden. Die zugrundegelegten Studien enthalten hierüber keine Aussagen, da sie nicht mehr als klinische Parameter zur Einschätzung nutzen. Dies wird der Diagnose nicht gerecht, die als solche nur fachärztlich nach Untersuchung des Organs gestellt werden kann.

Die eingehende HNO-ärztliche Untersuchung ist zur feineren Diagnose deshalb unentbehrlich, gerade um eine Therapieentscheidung vorzunehmen.

Eine reine akute Laryngitis ist daher eher m.E. eine absolute Ausnahmediagnose. In der Klinik stufen wir sie als Rhinopharyngolaryngitis oder oft zwangsläufige Beteiligung des Kehlkopfes als anatomische Schnittstelle einer Rhinosinubronchitis ein. Hierdurch wird deutlich, dass die Beteiligung des Kehlkopfes bei einer viralen Infektion der Atemwege nur Teil eines Krankheitsbildes ist, deren Verlauf häufig biphasisch ist und es im weiteren regelmäßig zu einer bakteriellen Superinfektion mit einer Ausweitung auf die oberen und unteren Atemwege kommt. Die entsprechenden Keimnachweise belegen diesen Aspekt und führen zu der auch nachvollziehbaren besseren Wirkung von Erythromycin als Penicillin V, das ein relativ enges Wirkspektrum besitzt. In der klinischen Praxis hat sich eher Amoxicillin oder Azithromycin als Makrolidantibiotikum durchgesetzt.

Wir wissen nicht, warum viele Patienten primär im Rahmen einer common cold mit einer Heiserkeit reagieren. Anscheinend gibt es im Atemwegssystem individuelle Prädilektionsstellen, die abhängig sind von dem Erregerspektrum, bekannten Vorerkrankungen wie Allergien, Asthma und chronischen Sinusitiden. Diese gehören zur notwendigen Differenzialdiagnostik.

Ebenso werden häufig wichtige Differenzialdiagnosen bei einer HNO-ärztlichen Untersuchung ausgeschlossen etwa die Stimmbandparese (nicht selten als primäres Symptom eines Bronchialkarzinomes), Zufallsbefunde wie Stimmbandknötchen, Intubatonsgranulome oder eine Laryngitis posterior bei einer Refluxgastritis.

Dagegen erscheint der lupenlaryngoskopische Befund bei einer rein akuten Laryngitis zumeist unauffällig und ist damit eher charakteristischer Befund und Teil der Diagnosestellung. Häufigste mikroskopisch sichtbare Veränderung abhängig vom Krankheitsstadium ist eine streifige Rötung und Gefäßinjektion der Stimmbänder. Hinzuweisen ist auch auf eine Monochorditis bei einer Tuberkulose.

Die HNO-ärztliche Untersuchung einschließlich der Endoskopie der Nase und des Kehlkopfes führt durch die Zusammenschau der Befunde auf die Fährte und ermöglicht eine zielgerichtetere Therapieentscheidung, die primär die Vermeidung unnötiger Antibiotikatherapien zum Ziel hat, oft aber ohne diese nicht auskommt, da die prognostische Einschätzung des Krankheitsverlaufes das Alter, den Immunstatus, Nikotinabusus, Begleiterkrankungen wie OSAS und COPD, relative Mundtrockenheit vor allem durch gleichzeitige Einnahme von Antihypertensiva oder vorbestehende Kehlkopferkrankungen mit einschließt.

Erwartungshaltungen während der zwar selbstlimitierenden, aber doch bis zu 14 Tagen und mehr relativ protrahiert verlaufenden Erkrankung wecken dabei bei den Patienten den Wunsch nach einer zusätzlichen Antibiotikatherapie. Dabei werden entsprechende Wirkspiegel systemischer Applikationen aufgrund der eher spärlichen Durchblutung der Stimmbänder schwer erreicht.

Wichtigste Therapie ist bei der akuten Laryngitis die absolute Stimmruhe gerade in Sprechberufen und die Befeuchtung der Atemwege durch Inhalationen, die durch Mukolytika, Salbei und Thymian ergänzt werden kann und zu einer Beruhigung der den Kehlkopf umgebenden Schleimhaut führt und als symptomatische Behandlung die subjektiven Beschwerden lindert. Nach begleitenden Risikofaktoren sollte daher bei eingehender Untersuchung gefahndet und diese mit in die Überlegungen bei der Indikation einer Therapie mit einbezogen werden.

Es fehlen darüber hinaus Daten, die belegen, inwieweit eine frühzeitig einsetzende Antibiotikatherapie beispielsweise gerade bei älteren Patienten eine Pneumonie abwenden kann.

Da die vorliegenden Ergebnisse der Cochrane Library auch zunehmend Eingang finden in die evidenzbasierte Medizin, die als Grundlage für die weitere Patientenversorgung dient, sollten hier vor einer generellen Aussage die erforderlichen differenzialdiagnostischen Überlegungen Eingang finden. Heiserkeit als Symptom ist kein alleiniges Kriterium für die Beurteilung einer Erkrankung. Aufgabe der guten klinischen Praxis kann es werden, die Patienten im Rahmen von Behandlungsprotokollen im Hinblick auf die notwendige Betrachtung der einzelnen Begleitfaktoren zu begleiten und hierüber mehr notwendige Aussagen im Hinblick auf die verbesserte evidenzbasierte Behandlung von Erkrankungen treffen zu können. Hierzu bietet die Cochrane Library eine gute Diskussionsgrundlage.

Dr. Hans Christoph Reeker,
ENT Specialist

I agree with the conflict of interest statement below:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

Thank you for your feedback on the Cochrane review *Antibiotics for acute laryngitis in adults.* We have updated the review and addressed your comments regarding the problems of a precise diagnosis for acute laryngitis.

Contributors

Feedback comment kindly translated by Toby Lasserson and checked by Dr. Hans Christoph Reeker.
Feedback reply by Ludovic Reveiz and Andres Cardona.

WHAT'S NEW

Date	Event	Description
3 February 2015	New citation required but conclusions have not changed	Our conclusions remain unchanged.

Date	Event	Description
16 December 2014	New search has been performed	Searches updated. We identified one new randomised controlled trial (Rafalskiy 2012).

HISTORY

Protocol first published: Issue 2, 2004
Review first published: Issue 1, 2005

Date	Event	Description
30 December 2013	New search has been performed	Searches updated. There were no new included or excluded trials to add to the review.
27 February 2013	Feedback has been incorporated	Feedback and reply included in this update.
30 January 2013	New citation required but conclusions have not changed	Our conclusions remain unchanged.
6 October 2010	Amended	Contact details updated.
21 January 2010	Amended	Contact details updated.
8 May 2009	Amended	Contact details updated.
22 November 2008	New search has been performed	Converted to new review format.
19 November 2008	New search has been performed	We updated the searches in November 2008. There were no new included or excluded trials to add to the review.
17 December 2006	New search has been performed	We updated the searches in December 2006. There were no new included or excluded trials to add to the review.
23 June 2004	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Ludovic Reveiz (LR), Andrés Cardona (AC) and Edgar Ospina (EO) initiated, designed and conducted the study.
Ludovic Reveiz and Andrés Cardona provided methodological perspectives and techniques for writing the protocol and the review.
An update was performed in December 2006. Ludovic Reveiz and Andrés Cardona evaluated the titles and abstracts from the search. All the review authors contributed to manuscript revision.
An update was performed in November 2008. Ludovic Reveiz and Andrés Cardona evaluated the titles and abstracts from the search. All the review authors contributed to manuscript revision.
An update was performed in January 2013. Ludovic Reveiz and Andrés Cardona evaluated the titles and abstracts from the search. Both the review authors (LR, AC) contributed to manuscript revision.
An update was performed in January 2014. Ludovic Reveiz and Andrés Cardona evaluated the titles and abstracts from the search. Both the review authors (LR, AC) contributed to manuscript revision.

DECLARATIONS OF INTEREST

Ludovic Reveiz: has contributed to this review in a personal capacity and during his spare time. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the Pan American Health Organization where he works.
Andrés Felipe Cardona: none known.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

A number of methods planned in the protocol could not be implemented due to the lack of data but may still be applicable for future versions of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Anti-Bacterial Agents [*therapeutic use]; Clarithromycin [therapeutic use]; Depsipeptides; Erythromycin [therapeutic use]; Fusarium; Laryngitis [*drug therapy]; Penicillin V [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans